India's health biotech sector at a crossroads

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India's home-grown biotech companies must strike a balance between domestic and international markets.

Indian biotech is at a crossroads. It must not only address the significant health needs of its domestic population, but also position itself to take advantage of the often more profitable global marketplace. The country's health biotech companies operate in close proximity to the shocking disparities in health that plague our globe today. Although these firms are uniquely suited to address these needs, they require financial and political support before they will commit to doing so.

In earlier studies, we examined the health biotech innovation systems of seven developing countries, including India[1,2]. One of the conclusions concerning the Indian health biotech system was that the expertise and efficiencies that reside in the domestic private sector are essential for the translation of knowledge into products and services for Indian citizens.

This study focuses on the private sector firms at the heart of innovation systems. To understand better the product development capabilities of India's nascent biotech sector and the strategies used by private firms to survive and grow amid a myriad of challenges related to operating in a developing world context, we studied 21 of the subcontinent's home-grown firms (**Supplementary Methods** online). The results reveal a sector preparing not only for future growth, but also, in some cases, for developing innovative products for global markets. To our knowledge, this is the first detailed, independent, publicly available research on health biotech firms in India based on face-to-face interviews with company representatives.

Shantha Biotechnics manufacturing facilities, Hyderabad.

The research is highly relevant to policy debates on development. A 2004 report by the United Nations Development Program (UNDP) argued that a strong private sector contributes to economic growth and reduces poverty[3]. The UNDP report did not focus on health issues, however, and more research is needed to understand how the domestic private sector can best be harnessed to address local health needs in developing countries.

We anticipate that the findings reported here will be of interest to biotech firms across the globe seeking partnerships with Indian firms, venture capitalists seeking investment opportunities, foundations interested in global health solutions and developing world governments seeking ideas about successful innovation strategies. On the basis of the data gathered here, we also present recommendations for India and other developing countries on how to encourage biotech firms to develop low-cost products relevant to domestic health needs. We hope this analysis will help to inform the debate on the contribution of biotech to health and economic development, and the concrete actions of those interested in innovation in developing and emerging economies.

Products and services

Our survey reveals that the Indian biotech sector offers a wide variety of products and services. We have sorted them into four major categories: affordable vaccines, nonvaccine therapeutics, innovative product development and contract services.

Affordable vaccines. Several Indian firms have focused their businesses on the development, manufacturing and marketing of vaccines

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Box 1 Case study: Shantha Biotechnics Private

Shantha Biotechnics (Hyderabad, India) is the first Indian biotech company to indigenously produce a recombinant DNA product, Hep-B vaccine. The company was founded in 1993 at Osmania University (Hyderabad) and later moved to the Center for Cellular and Molecular Biology (CCMB, Hyderabad) until an independent R&D facility was built. Currently, it enjoys a strong product portfolio (**Table 1**) and in August 2005 launched India's first indigenously developed 4-in-1 combination vaccine against diphtheria, tetanus, pertussis and hepatitis B. This year, it expects to launch a pentavalent version of this vaccine that will include protection against *H. influenzae* type b. Shantha had revenues of ~$16 million in 2004–2005, an increase of 75% over the same period from the year previous and targets ~25% of revenues toward R&D[15].

In 1995, H.E Yusuf Bin Alawi Abdullah, Foreign Minister of Sultanate of Oman, along with other friends, invested in the company, and helped Shantha obtain long-term, low-interest loans from Oman International Bank (Muscat, Oman). In the year 2000, private equity investors Morgan Stanley (New York) and the State Bank of India Mutual Fund (Mumbai, India) entered a small private round of equity raising and invested just over $10 million. Through these investments, bank loans and some loans from the Indian Department of Biotechnology's Technology Development Board, the company has been able to invest ~$40 million into its facilities and operations thus far. It has grown into an integrated biotech company, involved in all aspects of drug development. Over 60% of its revenues originate from exports, most of which are purchased by the Pan American Health Organization and UNICEF. Shantha has several manufacturing facilities some of which are certified by WHO, EMEA and FDA. At the close of 2006, the French healthcare company Merieux Alliance (Lyon, France) picked up a 60% stake ownership in the company.

Throughout the years, Shantha has adopted a cost-saving strategy through public-private collaborations, necessitated in part by the lack of direct government support for private research. For example, the Hep-B vaccine was developed in collaboration with the CCMB. Other collaborations include working with the International Centre for Genetic Engineering and Biotechnology, Indian Institute of Science, National Institute of Immunology, Indian Institute of Chemical Biology, National Centre for Cell Sciences, Bhabha Atomic Research Centre and some universities (**Table 4**). The nature of these relationships varies from close collaboration on specific projects to those where Shantha financially supports research with the prospect of identifying novel drug targets or candidates. The company has also entered into several collaborative partnerships with foreign entities (**Table 5**) in an attempt to accelerate development of novel and proprietary products.

(**Table 1**). India's first domestically produced and marketed recombinant DNA product was Shanvac-B, a recombinant human hepatitis B surface antigen (Hep-B) vaccine from Shantha Biotechnics (Hyderabad) (**Box 1**) that was launched in 1997. Shantha's innovative and efficient manufacturing process in the *Pichia pastoris* expression system drove down the cost of the vaccine. Several other domestic producers of Hep-B vaccine have since entered the local market to meet the demand for this product (**Table 1**). The entrance of domestically manufactured products into the marketplace and the local competition that followed has benefited Indian citizens in a 30-fold price reduction from that of the imported product (from ~$15 to ~$0.50), which was the only Hep-B vaccine previously available in the Indian market.

The impact of affordable vaccines has been felt both in India and abroad. For instance, Shantha Biotechnics now supplies nearly 40% of the United Nations Children's Fund's (UNICEF) global requirement for Hep-B vaccine, which is distributed in many countries, including those in Africa and Latin America. The Serum Institute of India (Pune) is not only the largest vaccine supplier to the government of India's expanded program on immunization (EPI), it is also India's largest exporter of vaccines with a 138-country distribution network. The company claims to be the world's largest manufacturer of measles and the diphtheria, pertussis, and tetanus (DPT) group of vaccines and through its relationships with UNICEF and the Pan American Health Organization provides vaccines for 50% of children immunized globally. Likewise, New Delhi–based Panacea Biotec supplies its oral polio vaccine to India's expanded program on immunization and to UNICEF.

Nonvaccine therapeutics. The Indian population has also reaped significant benefits from the process efficiencies and cost-effective manufacturing of domestic firms, resulting in the availability of affordable, indigenously produced biopharmaceuticals. For example, Biocon (Bangalore) has developed a proprietary process for manufacturing recombinant human insulin. Even before Biocon's product (Insugen) entered the domestic market, international competitors reduced the price of their imported products by nearly 40%. Biocon priced their product even lower still and claims that Insugen remains the most affordable human recombinant insulin product in the Indian market. Shantha Biotechnics priced their recombinant interferon alpha (IFN-α) product Shanferon at 300 rupees (~$6.50), a drastic reduction from the previous market price of 1,200 rupees (~$26).

If the above trend continues, the cost of biopharmaceuticals produced by both domestic and overseas suppliers will continue to decrease as more domestic companies manufacture these products locally. Currently, from the companies we surveyed, Wockhardt, (Mumbai), Biocon, Shantha, Bharat Biotech International (Hyderabad), Transgene Biotek (Hyderabad) and Dr. Reddy's Laboratories (Hyderabad) are among the domestic manufacturers of recombinant drugs, such as insulin, erythropoietin, streptokinase, interferons and granulocyte colony stimulating factor (**Table 1**). The global market for such generic biopharmaceuticals is expected to increase significantly in the next few years as several 'blockbuster' drugs lose patent protection[4]. Indian companies appear well positioned to leverage their cost-effective manufacturing capabilities to corner some of this market share and compete on a global scale.

In their efforts to develop broad manufacturing capabilities, several Indian firms have invested in new manufacturing facilities to expand their capabilities for scale-up (e.g., in bacterial, fungal or mammalian expression systems) in a variety of formulations. These facilities are being refurbished or built in accordance with the standards of international regulatory agencies, such as the US Food and Drug Administration (FDA), European Medicines Agency (EMEA) and the World Health Organization (WHO), to facilitate access to international markets not only for biogenerics but also novel protein products currently in their pipelines (**Table 1**).

Novel product development. Indian firms are also beginning to make inroads into innovative health product discovery and development. As of January 1, 2005, India has adopted changes in its patent regime to include product patents, thus complying with the World Trade Organization's Trade Related Aspects of Intellectual Property (WTO-TRIPS) agreement. This change in the intellectual property (IP) regime has prompted many of India's vaccine companies to dedicate innovative research

Table 1 Indian health biotech firms interviewed and their product/technology portfolios[a]

Company name	Products/technologies on the market[b]	Products in development	International quality certification
Avestha Gengraine Technologies	A number of health foods, agbiotech and nutraceutical products and technologies. Also provides services such as plant genetic engineering for salt, drought and disease tolerance	Ten to eleven biosimilars, tuberculosis diagnostic microarray chip	—
Bharat Biotech International	Products include INDIKINASE (recombinant streptokinase for myocardial infarction), REGEN-D (recombinant epidermal growth factor for foot ulcers), ZELECT (oral rehydrating salts + zinc for treatment of diarrhea), Revac-B (recombinant Hep-B vaccine), BIOPOLIO (oral poliomyelitis vaccine), BIOGIT (yeast probiotic), BIO-ENOX (enoxaprin sodium injection) HEPASOLV heparin sodium injection	Vaccines (Japanese encephalitis, malaria (four strains), rabies, and rotavirus (two strains), avian flu, *S. aureus*); biotherapeutics (probiotic and antibiotic combinations and lysostaphin)	Korean FDA and WHO GMP certification
Bhat Bio-Tech India	Thirty-eight diagnostic tests, including blood grouping sera, urinalysis, hepatitis B and C, pregnancy, HIV, malaria, dengue and cancer markers; and recombinant proteins	Hep-B vaccine, insulin, tissue plasminogen activator (tPA), streptokinase, growth factors, interleukins, cardiac markers, PCR kits for detection of pathogens and other test kits (e.g., HIV-HCV combo test, pregnancy)	ISO 9001, ISO 13485 and GMP certified
Bharat Serums and Vaccines	Over 25 brands in several areas including plasma derivatives, monoclonals (anti Rho-D immunoglobulin), equine antitoxins and antisera, cardiovascular disease (streptokinase and urokinase), antifungals (amphotericin-B lipid complex and deoxycholate), anesthetics and hormones (human chorionic gonadotropin and follicle stimulating hormone)	Recombinant rotavirus antibody, mAb against tetanus, recombinant rabies vaccine, novel liposomal drug delivery systems, novel formulation for amphotericin (antifungal and leishmaniasis drug), and lipid-free propofol	WHO GMP certification
Biocon	A host of industrial enzymes, marketed globally. Therapeutic products include: five generic statins, and a number of products for diabetes including Insugen, a recombinant human insulin.	Recombinant protein therapeutics including oral insulin, monoclonal antibodies, erythropoietin (EPO), granulocyte colony-stimulating factor (g-CSF), streptokinase and human growth hormone	ISO 9001, GMP, approved by US FDA, College of American Pathologists (CAP)
Biological E	500 products for various indications including gastrointestinal, respiratory, cardiovascular, antidiarrheal, antiinfectives and allergy medications as well as vaccines (tetanus toxoid, DPT, diphtheria toxoid, r-Hep-B) and antitetanus and antisnake venom sera	A host of vaccines including a tetravalent dengue vaccine, Japanese encephalitis, Hib conjugate, rotavirus, cholera, meningitis, measles and DPT-hep-B combination vaccines	Production facilities conform to GMP standards
Dr. Reddy's Laboratories	Several products marketed internationally (e.g., ~11 products in the US and ~30 in the EU) including g-CSF, doxofylline (asthma medication) and GRAFEEL (hG-CSF for cancer patients suffering from chemotherapy-induced neutropenia)	Phase 1 completed in Canada for a leading compound targeted for the treatment of blood lipid dysfunction and clinical development of a cardiovascular drug candidate is underway in Ireland	FDA-approved manufacturing facilities for various products
GangaGen Biotechnologies	No products on the market as of July 2006.	Antibacterials for human diseases (such as tuberculosis), staphylococcal nosocomial interventions, and animal health and environmental products.	—
Indian Immunologicals	Sixteen products produced in-house including foot-and-mouth disease vaccine, human rabies vaccine, recombinant hepatitis B vaccine, and several animal and human-health products.	Pediatric and childhood vaccines, r-hep-B, DPT, hepatitis E vaccines and a novel DNA-based vaccine for rabies	ISO 9002 & WHO GMP Certification
LifeCare Innovations	Fungisome (lysosomal-mediated delivery of amphotericin B for treatment of fungal or leishmania cells) and Fungitericin (amphotericin B for treatment of systemic mycosis and visceral leishmaniasis), Fungitrace (itraconezole; oral antifungal for subacute and chronic infections), Psorisome (dithranol; topical treatment for psoriasis)	Drug candidates for psoriasis and TB (based on their lysosomal drug delivery system) are entering phase 1	Production facilities conform to GMP standards
Nicholas Piramal India	Two hundred and fifty different brands, some of which are produced for export. The products cover a large number of indications in addition to diagnostics and vitamins	A cdk4 inhibitor for cancer treatment is in clinical trials in Canada and India. Has an anti-fungal herbal product in phase 2 and a drug candidate against methicillin resistant *Staphylococcus aureus* and vancomycin resistant enterococcus in late pre-clinical development.	Manufacturing plant approved by US FDA, MCA of UK, TGA of Australia and the European and Canadian Drug Authorities
Panacea Biotec	Vaccines (oral polio, Hep-B, Hep-B+DPT, Hib+DPT, Hep-B+DPT+Hib), and over 40 drugs/formulations for at least ten human indications including pain management, diabetes and renal disease	Vaccines against dengue, Japanese encephalitis and anthrax	WHO GMP facility for vaccine production
Reliance Life Sciences	Blood plasma proteins, recombinant proteins, DNA-based diagnostic testing services, cytogenetic testing services, plant products and software to manage clinical trials	Working on products in several areas including stem cell therapeutics, monoclonal antibodies and novel proteins	GMP facility for recombinant protein production
Serum Institute of India	Manufacture and marketing of 15–20 products, for domestic and international markets. Products include antisera (polyvalent anti-snake venom), vaccines (MMR, DPT, r-Hep-B vaccines and others)	DNA-based rabies vaccine, a novel peptide vaccine for measles, DPT/Hep-B combination vaccine and a pentavalent vaccine by combining the latter with *Haemophilus influenza* type b vaccine	WHO GMP certification

Table 1, continued Indian health biotech firms interviewed and their product/technology portfolios[a]

Company name	Products/technologies on the market[b]	Products in development	International quality certification
Shantha Biotechnics Pvt.	r-Hep-B vaccine, r-INFα-2b), r-streptokinase, r-EPO, combination vaccine DPT/Hep-B, and a few diagnostic kits	Typhoid and Japanese encephalitis vaccines, a pentavalent vaccine (DPT+Hep-B+Hib), insulin, growth factor and human monoclonal antibodies for four oncology indications	WHO GMP certification
Strand Life Sciences	Products include Admetis (platform for modeling and predicting drug-relevant properties of molecules *in silico*), Avadis (technology platform for data analysis and visualization), and target-focused synthetic compound libraries	Bioinformatics-based toxicity prediction software for novel drug development and next generation bioinformatics software tools for Affymetrix arrays	—
Transgene Biotek	Some technologies and products ready to be outlicensed including a novel drug-delivery technology (for insulin and Hep-B), and three biogenerics (pegylated-EPO, r-tPA, and pegylated-INFα-2b)	Meningococcal meningitis polyvalent conjugate vaccine, recombinant meningococcal meningitis B vaccine, Hib conjugate vaccine, hepatitis-B vaccine (oral delivery) and transgenic rabies vaccine, interferon β 2b and γ, and two cancer drugs for colon and breast cancers using short interfering RNA (siRNA)-targeted approach	—
Wockhardt	Hep-B vaccine, EPO, insulin, an automatic insulin delivery injection pen, interferon (INFα-2b), granulocyte g-CSF and glargine (a long-acting insulin analog)	Twenty-five products (mostly generics, for various indications including anemia, diabetes and antivirals) in various approval phases in various countries including recent approval from the US FDA for marketing cefuroxime axetil and Zonegran (zonisamide).	Manufacturing plants approved by various regulatory agencies including TGA of Australia, US FDA, and UK's MHRA
Exclusive service companies and services provided			
Clinigene	Contract clinical trials services	N/A	College of American Pathologists (CAP)
SIRO Clinpharm	Contract clinical trials services	N/A	—
Syngene	Contract services in basic research and synthetic chemistry	N/A	ISO 14000

[a]As of July 1, 2006 [b]For the sake of completeness, both biological and pharmaceutical products are listed in some cases. EPO, erythropoietin; INF Interferon; DPT, diphtheria, pertussis, tetanus; FSH, follicle-stimulating hormone; HCG, human chorionic gonadotropin; g-CSF, granulocyte colony stimulating factor; GMP, good manufacturing practice; Hib, *H. influenzae* type B; MMR, measles, mumps, rubella; WHO, World Health Organization; tPA, tissue plasminogen activator.

programs to the development of combination vaccines (**Table 1**). For example, Shantha Biotechnics and the Serum Institute of India are both working to develop a pentavalent vaccine to protect against five infectious agents, including DPT, Hep-B and *Haemophilus influenzae* type b (Hib). Other companies that are developing single or combination vaccines, against locally relevant diseases like Japanese encephalitis, cholera and meningitis include Panacea Biotec, Biological E (Hyderabad) and Transgene Biotek. With financial support from the Bill and Melinda Gates Foundation (Seattle, WA), Program for Appropriate Technology in Health (PATH; Seattle, WA), Malaria Vaccine Initiative (Bethesda, MD) and the European Malaria Vaccine Initiative (Copenhagen, Denmark), Bharat Biotech International is currently developing four vaccine candidates against malaria and two against rotavirus. The funding agencies themselves are driving the company to innovate under the condition that a successfully developed vaccine must be made available at an affordable price.

Indian firms are also making directed attempts to produce novel nonvaccine products. For instance, the small firm GangaGen Biotechnologies (Bangalore) is a purely research-driven company focused on developing bacteriophages as antibacterial treatments to help address issues related to multi-drug-resistant bacteria. Bharat Biotech International has filed an Investigational New Drug application (IND) for lysostaphin, an anti-infective for multi-drug-resistant *Staphylococcus aureus*, and is marketing epidermal growth factor (REGEN-D) for the novel indication of treating bed sores and diabetic foot (epidermal growth factor was previously used in the treatment of burn victims, a traditionally small market). Several Indian firms are also trying to develop products targeted to diseases of particular relevance to developing countries, such as malaria, tuberculosis, HIV, leishmaniasis and meningitis (**Table 1**). These companies include LifeCare Innovations (New Delhi), Bharat Serums and Vaccines (Mumbai), Bhat Bio-Tech India (Bangalore), Transgene Biotek and Nicholas Piramal (Mumbai). Dr. Reddy's Laboratories and others pursuing R&D programs in several diseases have set up subsidiaries or research groups outside of India to assist their efforts (**Table 2**).

Contract services. A few Indian firms are using a contract services approach to fund their operations and develop their commercialization capabilities. These services include R&D, clinical trials or manufacturing, and they are beneficial not only because they provide a financial resource, but also afford Indian companies access to valuable technology and expertise. For example, Avestha Gengraine (known as 'Avesthagen', Bangalore) aims to build the necessary infrastructure to become a fully integrated drug discovery company, in large part through contract services and collaborative arrangements with other organizations (**Box 2**). Syngene (Bangalore), part of the Biocon group of companies, focuses on contract services in basic research and synthetic chemistry and works primarily with major multinational corporations, such as Novartis (Basel) and Glaxo SmithKline (GSK; London). Other firms are using their additional manufacturing capacity to generate revenues through contract manufacturing services. One example is Bharat Biotech International, which through its contract for producing Wyeth's (Madison, NJ, USA) Hib vaccine, is the first vaccine manufacturer in a developing country to produce a foreign proprietary product. A successful partnership with a multinational corporation can greatly improve a young company's international credibility and may prompt negotiations with additional potential partners.

Some Indian contract research organizations are also improving their capabilities to conduct clinical trials locally. They maintain that the cost savings to major multinational corporations from conducting preclinical and early clinical investigations in India can effectively allow them to reduce the risk of larger investments in later stage, multicentric trials. Indeed, mul-

Table 2 Subsidiaries, joint ventures and research groups for companies interviewed

Company Name	Subsidiary or joint venture
Avestha Gengraine Technologies	JV with Meditab Specialties (an affiliate of Cipla) called Avesta Biotherapeutics and Research (Bangalore) was established in 2005 for pilot and commercial scale manufacturing of biotherapeutics products. Avesta Nordic (Bangalore) was established as a joint venture with the Center for Clinical and Basic Research (CCRB, Denmark) and IFU, a Danish investment fund to develop nutritional bioactive products for osteoporosis. Avesta Good Earth Foods was formed when Avesthagen acquired Good Earth Foods. This company sells nutraceuticals such as cereals and energy bars. Avesthagen was set up in 2003/04 as a subsidiary in San Diego
Bharat Serums & Vaccines (BSV)	BSV BioSciences subsidiary in San Jose, involved in early development of biotech products. Aims to eventually have regulatory capabilities. Joint venture with Zydus Cadila, one of the leading pharmaceutical companies in India, for the commercialization of a BSV's novel anticancer drug
Biocon	Syngene (subsidiary). Contract research for other companies. Clinigene (subsidiary). Contract clinical trials for major multinational corporations. Joint venture with the research institute CIMAB (Havana, Cuba) to develop antibodies and cancer vaccines. Recently acquired the US-based Nobex Corporation
Dr. Reddy's Laboratories	Perlecan Pharma was created in 2005 by Dr. Reddy's (with funding largely from Citigroup Venture and ICICI Venture), and although an independent company, will be involved in clinical drug development and out-licensing of Dr. Reddy's new drug candidates. Discovery unit in Atlanta (US). Agreement to purchase Roche's API business in Cuernavaca, Mexico. Joint venture with a company in China for marketing purposes
GangaGen Biotechnologies	GangaGen Biotechnologies is itself a subsidiary of GangaGen based in the US. GangaGen Life Sciences (Canada) is another subsidiary; works on development of phage-based products for eliminating human pathogens in food, animals and the environment
Indian Immunologicals	IndiaGen (joint venture in the business of animal breeding and genetics advisory services to improve productivity of milch cattle)
Nicholas Piramal India	WellQuest conducts clinical trials at the Wellspring Hospital in Mumbai. Pathlabs NPIL (majority stake in three pathlabs). Pathology and diagnostic labs, and an infertility center. Boots Piramal Healthcare. Joint venture between UK-based Boots and Nicholas Piramal India focusing on over the counter pharmaceutical segment. Allergen India is involved in ophthalmology solutions for the Indian market
Panacea Biotec	Joint venture (Chiron-Panacea Vaccines) for development and marketing of combination vaccines with Novartis Vaccines (UK). The venture currently markets five vaccines including some combination vaccines against Hep-B, Hib and DPT
Reliance Life Sciences	Reliance Clinical Services. A contract research organizations organization
Shantha Biotechnics	Shantha West (US subsidiary). Research on monoclonal antibodies for cancer treatment
Wockhardt	Wockhardt USA. Regulatory and intellectual property rights involved in generic pharmaceuticals in the UK and has a wholly owned subsidiary in Brazil. Majority-owned companies in South Africa and Mexico and marketing offices elsewhere. Joint venture with Representaciones E Investigaciones Medicas de C.V. (Mexico City, Mexico). Joint venture with Pharma Dynamics (Tokai, South Africa) to work on formulation for diabetes

ICICI, Industrial Credit and Investment Corporation of India.

tinational corporations are conducting more and more clinical trials in India and appear to be increasingly relying on Indian contract research organizations to manage these trials. SIRO Clinpharm (Mumbai), for example, conducts all Indian clinical trials for Covance (Princeton, NJ, USA), and has also dedicated ~100 employees to projects specific to Pfizer (New York). Clinigene (Bangalore), another Biocon subsidiary, is the first company in India to have a laboratory certified by the College of American Pathologists (Northfield, IL, USA), and it conducts trials for multinational corporations, such as Merck (Whitehouse Station, NJ, USA), AstraZeneca (London) and Pfizer. The knowledge generated from these partnerships is in turn being translated into innovation at home. Clinigene, for example, has developed one of the first diabetes registries in India in partnership with local research programs and hospitals. The registry was initiated by a client request and is currently being used to facilitate the testing of novel combinations of treatments for conditions, such as diabetic nephropathy.

The rapid increase in clinical trials conducted in India has caused some firms, including Wockhardt and Nicholas Piramal to ramp up their own capabilities in this area. Some Indian companies have developed significant domestic

Box 2 Case study: Avestha Gengraine Technologies

Avesthagen (Avesthagen, Bangalore) is a private, spin-off company from the National Center for Biological Sciences and the University of Agricultural Sciences in Bangalore. The company started in 1998 at Villoo Morawala Patell's laboratories and has since expanded to nearly 200 employees, with a long-term goal of becoming an integrated drug discovery company. Its initial agricultural biotech focus has since expanded to include pharmaceuticals and nutraceuticals. Avesthagen currently has significant in-house basic biology skills, employing over 130 employees in its R&D program. The company is also expanding its manufacturing facilities and has local partners for conducting clinical trials.

Patell's initial work was supported by several prestigious grants from institutions, such as the Rockefeller Foundation (New York), the Indo-French Center for the Promotion of Advanced Research (IFCPAR; New Delhi, India), and India's Council of Scientific and Industrial Research. In 2001, the company raised $2 million from Industrial Credit and Investment Corporation of India (Hyderabad) Ventures, Tata Industries (Mumbai) and Oriental Bank of Commerce (New Delhi). Other strategic investors include India's Godrej Industries (Pirojshanagar, India), Cipla (Mumbai, India) and France's bioMérieux (Marcy L'Etoile, France).

Because of financial limitations, Avesthagen relies on extensive domestic and foreign collaborations with companies and research institutions (**Tables 4** and **5**) to develop new products and apply novel processes to basic drug discovery. Its pursuit of collaborative codevelopment projects is designed to bolster the company's financial position in the longer term, through shared IP, manufacturing or marketing revenues. Currently, ~60% of its revenues come from pharmaceutical and diagnostics projects, 30% originate from the nutraceutical segment and 10% are derived from agricultural biotech products. The company is now in a position to invest in cash-poor foreign firms with innovative technologies to expand their product portfolios and has entered into a number of joint ventures (**Table 2**). In early 2005, it acquired Good Earth Foods (Bangalore, India) to expand its foray into branded nutraceuticals.

Authors with executives of Indian Immunologicals, Hyderabad. From left to right, Peter Singer, KV Balasubramaniam, VA Srinivasan, Abdallah Daar, and Sarah Frew.

clinical networks, including Biological E, which relies on its wide network of ~13,000 physicians and hospitals for its clinical trials, and Reliance Life Sciences (Mumbai), which has linkages to tertiary eye care and cardiac hospitals for its regenerative medicine program. It will be vital to the industry that Indian companies expanding their capabilities in clinical trials management pay close attention not only to good clinical practice guidelines, but also to bioethical principles, to provide a high level of care and protect the rights of patients.

Partnerships for innovation

The Indian biotech sector has yet to produce a truly innovative health product with the stamp 'Made in India'. In general, Indian firms are at a relatively early stage in their innovative R&D programs. Even so, many executives interviewed in this survey expressed a strong commitment to R&D (**Table 3**) and had a positive reaction to India's move towards becoming TRIPS compliant, insisting that both are necessary to inspire innovation among India's biotech firms.

Local collaborations. Increasingly, Indian health biotech firms are using strategic partnerships to expand their innovative capacity. One such partnership is the R&D collaboration with domestic research institutes (**Table 4**). These collaborations can provide training opportunities for in-house staff, improve access to research facilities and expensive equipment, expand clinical trials capabilities and provide access to government-sponsored research funds. For example, Panacea Biotec is currently scaling up production of a recombinant anthrax vaccine and a vaccine against Japanese encephalitis, which were products of collaborations with scientists from Jawaharlal Nehru University (New Delhi) and the Institute of Genomics and Integrative Biology (IGIB, formerly the Center for Biochemical Technology; New Delhi), and the National Institute of Immunology (New Delhi), respectively. Similarly, Dr. Reddy's Labs and Nicholas Piramal are among the many Indian firms sponsoring research projects at the Indian Institute of Science (IISc; Bangalore).

Table 3 Financial background for companies interviewed

Company name	Public or private	Approximate revenues 2004/05 ($ million)[a]	Approximate % of revenues from exports	Approximate R&D expenditure (% of total revenues)	Approximate total number of employees (and no. involved in R&D), where available
Avestha Gengraine Technologies	Private	N/A	N/A	N/A	200 (130)
Bharat Biotech International	Private	10	30	20	300 (50)
Bharat Serums and Vaccines	Private	19 (ref. 15)	N/A	9	520 (60)
Bhat Bio-Tech India	Private	1	60	20	65 (12)
Biocon[b] Syngene Clinigene	Public	180 15 (loss of 0.6)	58 100 Most	12 N/A N/A	2000 (750) 526 60
Biological E	Private	40	N/A	32	1100 (30)
Dr. Reddy's Laboratories	Public	440	66	14	6,000 (800–900)
GangaGen Biotechnologies	Private	0	N/A	N/A	28 (24)
Indian Immunologicals	Government owned	22[c]	8	5	680 (40)
LifeCare Innovations	Private	N/A	N/A	25	39 (7)
Nicholas Piramal India	Public	300	12	4	6175 (390)
Panacea Biotec	Public	120	8	5	2300 (280)
Reliance Life Sciences	Private	N/A	N/A	N/A	412 (128)
Serum Institute of India	Private	130 (ref. 15)	65–70	N/A	2,000
Shantha Biotechnics	Private	16 (ref. 15)	N/A	25	500 (70–80)
SIRO Clinpharm	Private	N/A	N/A	N/A	200
Strand Life Sciences	Private	N/A	100	N/A	75
Transgene Biotek	Public	0.5	N/A	N/A	150 (50)
Wockhardt	Public	300	60	N/A	(350)

[a]In some cases, revenues generated from the sale of biologicals and pharmaceuticals could not be determined separately, and the figures given are inclusive of the company's net activities. [b]Figures for Biocon are inclusive of Syngene and Clinigene [c]Data for 2005–2006.

Table 4 Alliances/collaborations between companies interviewed and domestic organizations

Company name	Indian alliances and objective
Avestha Gengraine Technologies	Collaboration with Cipla (Mumbai) to develop a number of biosimilar molecules to be marketed by Cipla. Working with state governments and public institutions such as CSIR for a variety of purposes and has a relationship with St. John's Medical Academy for conducting clinical trials. Collaborative research agreement with Ranbaxy (Gurgaon) for new drug development relating to construction of recombinant cell lines required for screening Ranbaxy's drug candidates. PhD training program with Mysore University
Bharat Biotech International	Received certain technologies from various domestic institutes such as the Indian Institute of Chemical Technology (IICT, Hyderabad). Developed lysostaphin with the Institute of Genomics & Integrative Biology (IGIB, New Delhi), a CSIR lab, through the New Millennium Indian Technology Leadership Initiative program. Work with All India Institute of Medical Sciences (AIIMS), New Delhi and Indian Institute of Science (IISc), Bangalore for development of rotavirus vaccine. Comarketing with Wockhardt, Intas, Nicholas Piramal, VHB and Lupin for various different products. Partnered with International Center for Genetic Engineering and Biotechnology (ICGEB) to develop a malaria vaccine
Bhat Bio-Tech India	Joint projects and PhD-training program with IISc and other institutions in Bangalore
Biocon	Provided some funding for XCyton Diagnostics (Bangalore), a diagnostics company
Biological E	Some work with IISc. Outsource IP work and data management for clinical trials to Indian agencies
Dr. Reddy's Laboratories	Sponsoring projects at various domestic institutions such as the IISc and IICT. Bhabha Atomic Research Centre (BARC, Mumbai) for access to radiation
Indian Immunologicals	Five-year collaboration with IISc for basic research, animal testing and DNA rabies vaccine. Collaborated with IISc (Bangalore) to develop world's first combination human rabies vaccine containing DNA vaccine and a low dose of cell culture vaccine. Outsources clinical trials to Indian contract research organizations
LifeCare Innovations	Post Graduate Institute of Medical Education & Research: Chandigarh Bio-chemistry Department. Collaborative development of anti-TB and other anti-infective controlled release pharmaceuticals and evaluation of antifungals at Mycology Division. Panjab University. Collaborative development of liposomal pharmaceuticals. SGS Medical College & KEM Hospital (Mumbai). Clinical studies and trials. AIIMS (New Delhi). Preclinical studies of antileishmanial drug delivery system. Indian Institute of Technology (Kanpur). Materials development. CellMax. Collaborative development and marketing of recombinant biotherapeutics and medical diagnostics
Nicholas Piramal India	Several collaborations with CSIR labs, NII, IGIB and National Institute of Oceanography, Regional Research Laboratory in Jammu. Collaboration with IISc for anti-infectives. Work with Anna University (Chennai) on use of traditional medicine for oncology and inflammation. Collaboration with CDRI for work on malaria and diabetes
Panacea Biotec	Technology transfer and vaccine development for recombinant anthrax vaccine, developed at Jawaharlal Nehru University through Biotech Consortium India. Technology transfer and vaccine development for Japanese encephalitis vaccine; developed at National Institute of Immunology. Technology transfer and development of foot-and-mouth disease vaccine developed by Indian Veterinary Research Institute, through National Research Development Corporation. Clinical trials done in a network of medical institutes through Indian contract research organizations
Reliance Life Sciences	Technology development partnerships with national institutes
Shantha Biotechnics	Working together with the Centre for Cellular & Molecular Biology (CCMB) for development of novel expression vectors. Financial support for scientists at the International Centre for Genetic Engineering and Biotechnology (ICGEB, New Delhi) for development of kinase inhibitors as cancer treatment. Collaboration with NII to develop vaccines based on nanotechnology. Some work conducted at BARC for developing plant-based products such as proteins and vaccines
Strand Life Sciences	St. John's Hospital (Bangalore) and Central Drug Research Institute (Lucknow) on hepatoxicity. Created a diabetic registry with Clinigene to gather serological data to profile patients at risk of developing nephropathy. Syngene is a synthesis partner for target focused molecular libraries. Work with CSIR labs on three-dimensional-visualization platform for bioprocesses
Syngene	IISc collaboration on expression in *Pichia pastoris.* Indian Association of Cultivation of Science (IACS, Calcutta) in synthetic chemistry. Links formed with public institutions to give scientists an outlet to be creative and explore subject areas of interest, provided these activities do not conflict with contract work conducted for their clients
Transgene Biotek	Collaborations with CSIR institute for the development of oral delivery platform technologies. Collaborative partnership with an Indian university to develop transgenic rabies vaccine
Wockhardt	Joint research programs with universities and research institutes as well as production and operational relationships with other firms

CSIR, India's Council of Scientific and Industrial Research.

Several R&D partnerships are directly focused on developing products that address India's local health needs. For instance, Indian Immunologicals (Hyderabad) is collaborating with IISc for basic research and animal testing of its DNA rabies vaccine and Bharat Biotech International has partnered with the International Centre for Genetic Engineering and Biotechnology (ICGEB; New Delhi) and the IGIB to develop vaccines against malaria and rotavirus, respectively. Bharat has also worked with other laboratories of India's Council of Scientific and Industrial Research (New Delhi) through the New Millennium Indian Technology Leadership Initiative program, as has Strand Life Sciences (Bangalore), Avesthagen and Nicholas Piramal. The New Millennium Indian Technology Leadership Initiative program aims to bring together private firms, national R&D laboratories and academia to develop products of national relevance (http://www.csir.res.in).

Some firms, such as Bhat Bio-Tech India and Avesthagen, are collaborating with Indian universities to advance training and help develop a specialized and qualified work force in biotech. For example, employees at Avesthagen are encouraged to pursue doctoral studies through a collaborative program at Mysore University (Mysore). In turn, students at the university working on Avesthagen-sponsored research projects have the opportunity to join the firm later on.

Curiously, very few codevelopment partnerships are taking place between Indian firms themselves. A notable example, however, is the strategic alliance that combines Clinigene's serological data from local diabetic registries with Strand Life Sciences' proprietary data-mining tool and analytical expertise, to identify biomarkers for groups at high risk of developing diabetic nephropathy. The two firms jointly filed for a patent for the biomarkers in the United States.

International collaborations. Several Indian firms are currently developing vaccines based upon technology transferred from abroad and more are looking to foster such relationships

(**Table 5**). For example, Nicholas Piramal, Bharat Biotech International and the Serum Institute of India have all licensed various vaccine technologies from institutions in Canada, the United States and the Netherlands. Also, Biological E is working with technology from the International Center for Diarrheal Disease Research, a UNICEF organization based in Bangladesh, to develop a vaccine for cholera.

Collaboration between Indian firms and global health foundations and initiatives are another form of partnership that can facilitate development of health products relevant to the developing world. The firms are interested in working with these groups for access to their expertise and resources in tackling global health issues. For instance, Bharat Biotech International is manufacturing *Plasmodium vivax* and *Plasmodium falciparum* proteins and developing four vaccine candidates for the Malaria Vaccine Initiative and the

Table 5 Collaborations/partnerships between companies interviewed and foreign entities

Company name	Alliances and their objectives
Avestha Gengraine Technologies	Collaboration with bioMerieux (Marcy L'Etoile, France) for co-development of diagnostic chips for tuberculosis. Working with Sequenom (San Diego) for validation of genetic markers for breast cancer, lung cancer and diabetes. Co-development of medicinal plants with Nestle Nutrition (Vevey, Switzerland) and discovery of plant based nutraceuticals for osteoporosis with the Center for Clinical and Basic Research (Ballerup, Denmark). Collaboration with Imperial College (London), research into the genetic analysis of systemic lupus erythematosus (SLE). Collaborative research with AstraZeneca (London) on *Mycobacterium tuberculosis* (the causative agent of TB). Agreement with TNO Quality of Life (Leiden, The Netherlands) to develop therapeutics targeted at obesity
Bharat Biotech International (BBIL)	Contract manufacturing with Wyeth (Madison, NJ USA) for HibTITER. This also let BBIL become the first Indian Bio-Pharma company to be approved by the Korean FDA. Contract manufacturing and marketing for the investigational Japanese encephalitis vaccine with Acambis (Cambridge, UK). Rotavirus, typhoid and rabies vaccine clones were developed with help from the US National Institutes of Health (Bethesda, MD US). Strategic alliance with Novavax (Rockville, MD, US) to pursue the rapid development of pandemic influenza vaccine for India and other Association of Southeast Asian Nations (ASEAN) markets.
Bharat Serums & Vaccines	Marketing and distribution of drug portfolio with two US-based companies. Co-developed a novel formulation for an anti-fungal (amphotericin) with a company in the US. Some molecular characterization work through Northern Lipids (Vancouver)
Biocon	Co-development of human antibodies with Vaccinex (Rochester, NY US). Co-development of oral insulin with Nobex (Research Triangle Park, NC, US), which it recently acquired. Strategic alliance with Karolinska Institute (Solna, Sweden)
Biological E	Collaboration on Hib conjugate vaccine with RIVM (Bilthoven, The Netherlands). Technology transfer agreements with two research institutes in China and collaboration with a Chinese company for hepatitis A vaccine, EPO and g-CSF. Agreement with Intercell (Vienna) to develop, manufacture and sell Intercell's Japanese encephalitis vaccine in Asia. Developing cholera vaccine with clone in-licensed from the International Centre for Diarrheal Disease Research (Dacca, Bangladesh)
Clinigene	Conducting two phase 3 studies for Merck in the US
Dr. Reddy's Laboratories	Co-development and commercialization of balaglitazone (for type 2 diabetes) with Rheoscience (Rødovre, Denmark). Development and marketing of 11 generic pharmaceuticals with Pharmascience Group of Canada. Past relationship with InCyte Genomics (Wilmington, DE, US) for data mining to discover targets for diabetes
Indian Immunologicals	Collaborative project for the production of human monoclonal antibodies with Thomas Jefferson Medical School (Philadelphia). Collaborated with Harvard Medical school (Boston) to develop polysaccharide vaccines. Past collaboration with the Wellcome Foundation (London) to build company's plant at Hyderabad. Marketing agreement for rabies vaccine with Pfizer (New York, New York, US) in South East Asia
Lifecare Innovations	Collaboration with the Council for Scientific and Industrial Research (Pretoria, South Africa) led-consortium for clinical development and commercialization of a sustained release PLG (poly DL-lactide-co-glycolide) anti-TB product
Nicholas Piramal India (NPIL)	Marketing biotechnology products for Hoffman-La Roche(Basel), Gilead Sciences (Foster City, CA US), Chiesi Farmaceutici (Parma, Italy) and Genzyme (Cambridge, MA US). NPIL to provide process development and scale-up/manufacturing services to Pfizer's animal health division and other major pharma companies. NPIL to manufacture and supply select hospital care products for a large global hospital products company. Licensed vaccine technology from Canada's National Research Council (Ottawa)
Panacea Biotec	Co-development of non-refrigerated vaccines with Cambridge Biostability (Cambridge, UK). Collaboration with a leading European multinational corporation on an anti-hypertensive drug candidate using Panacea's drug delivery technology. Technology transfer from the US National Institute of Health for development of a peptide for human hair growth
Serum Institute of India	Worked with Netherlands-based National Institute for Public Health and the Environment (RIVM) to develop its Hib vaccine
Shantha Biotechnics	Co-development of cholera and typhoid vaccines with International Vaccine Institute (Seoul). Shantha distributing Japanese encephalitis vaccine in India for GreenCross Vaccine (Yongin-Si, Korea). Distribution of Hep-B vaccine in US through Spectrum Pharmaceuticals (Irvine, CA, US) and meningitis vaccine in India through Baxter (Deerfield, IL, US). Shantha's 'Hepashield' was marketed through Pfizer in the past. Co-development of heat-stable vaccines with Cambridge Biostability. Technology transfer agreement with Polytherics (London) to develop a PEG-interferon product (for hepatitis C). Agreement with a large European company to co-develop pentavalent vaccines
SIRO Clinpharm	Conducts clinical development work for Pfizer and Covance (Princeton, NJ US)
Strand Life Sciences	Contract development of software with Affymetrix (Santa Clara, CA US) for their microarray analysis systems. Marketing relationship wtih CombiMatrix (Mukilteo, WA US) to market Strand's flagship software (Avadis) for microarray analysis. Partnership with MediBIC Alliance (Tokyo) to develop bioinformatics solutions for Japanese companies. Partnership with BioRad (Hercules, CA, US) for its predictive ADME unit. Co-development of bioinformatics software tools for Affymetrix arrays with Stratagene (La Jolla, CA, US). Collaborative research with Elan Pharmaceuticals (Dublin). Distribution of Acuris, a bioinformatics tool to automate gene and protein annotation, through UBI (Calgary, Canada)
Syngene	Work on bacterial virulence factors with Innate Pharmaceuticals (Umea, Sweden). Working on TB with a Singapore-based group. Doing some work for GlaxoSmithKline in the UK.
Transgene Biotek	Phase 3 clinical trials for quadrivalent meningococcal vaccine conducted in Africa through partnership with a US-based company. Co-development with a US-based company for cancer drugs based on siRNA
Wockhardt	Collaboration regarding Wockhardt's hospital business with Howard Hughes Medical Institute (Chevy Chase, MD, US). Manufacturing agreements with AstraZeneca's Cell Therapeutics (Seattle, WA US), Sanofi-Aventis (Paris), Aguettant (Lyon, France), Schering-Plough (Kenilworth, NJ US) and Eisai (Tokyo)

European Malaria Vaccine Initiative, and the Serum Institute of India is in discussions with Global Alliance for Vaccines and Immunization (Geneva, Switzerland) for global distribution of its Hib vaccine.

Entering into codevelopment projects with foreign firms is yet another strategy for Indian companies to set the stage for innovation by gaining access to valuable skills, expertise and proprietary technology. Biocon, for example, is developing human monoclonal antibodies (mAbs) with Vaccinex (Rochester, NY, USA), and after funding a project with Nobex (Research Triangle Park, NC, USA) to develop oral insulin, recently acquired this company in its entirety. Other firms also expressed willingness to invest in cash-starved foreign firms with innovative technologies. Avesthagen, for example, has entered into several collaborative projects, and is particularly interested in those where the IP generated from the project is shared (**Box 2**). **Table 5** demonstrates some of the existing collaborations and codevelopment projects between Indian firms and their foreign counterparts. Codevelopment of products and technologies is sometimes mediated through joint ventures between Indian and foreign organizations (**Table 2**). For example, Panacea-Chiron Vaccines is a joint venture between Panacea Biotec and Novartis Vaccines (Cambridge, MA, USA) focused on developing combination vaccines. Biocon has also formed a joint venture agreement with the Cuban pharmaceutical group CIMAB to develop human mAbs in cancer. As a result of this partnership, Biocon Biopharmaceuticals, a joint venture between Biocon and CIMAB, has been set up for manufacturing of a broad range of novel and biosimilar therapeutic products.

Foreign firms interested in tapping into the large Indian market are partnering with local firms for their distribution networks and knowledge of the local regulatory landscape and legal system. Nicholas Piramal, for example, markets the biotech products of Roche (Nutley, NJ, USA), Gilead (Richmond, VA, USA), Chiesi (Parma, Italy) and Genzyme (Framingham, MA, USA) in India. Shantha Biotechnics distributes GreenCross Vaccine's (Gyeonggi-Do, Korea) Japanese encephalitis vaccine and Baxter's (Deerfield, IL, USA) meningococcal C vaccine in India. And Biological E is involved in the codevelopment, manufacture and distribution of Intercell's (Vienna) Japanese encephalitis vaccine across Asia.

Financial environment and business models

Indian companies currently involved in health biotech have entered this field by several different routes. Some of the larger biopharmaceutical companies in India were created when an existing parent company opted for the biotech segment as a viable investment strategy[5]. Companies following this strategy include Biocon (traditionally an industrial enzymes company) and Wockhardt (originally in the generics and hospital business). Nicholas Piramal (in real estate, glassmaking and textiles) and Dr. Reddy's (previously in generics) expanded into biotech primarily through acquisitions. Several of the smaller Indian biotech companies began their businesses with a focus on a particular niche area in the biotech arena, such as Bhat Bio-Tech India (diagnostics), Strand Life Sciences (bioinformatics) and SIRO Clinpharm (clinical research). Prominent among the dedicated and innovative health biotech startup companies that have managed to gain significant success and recognition are Bharat Biotech International and Shantha Biotechnics.

Bhat Bio-Tech India employees assembling HIV diagnostics, Bangalore.

Scarcity of risk capital investment in biotech has forced most of the Indian firms we studied to adopt a revenue-generating growth model from inception. In general, this has involved either a product- or service-based model or both. Many health biotech companies in India (e.g., Biocon, Reliance Life Sciences, Shantha Biotechnics, Wockhardt, Bharat Biotech International, Biological E, Nicholas Piramal and Avesthagen) rely on manufacturing of generics and/or contract services to generate revenues, which are then reinvested into R&D work in other areas. This reinvestment, however, is often diminished by loss of potential revenues when several domestic competitors compete on price (and thus drive down market prices).

Although many companies in India have adopted similar strategies, there are differences in how they raise the early capital necessary to develop initial capabilities. This is especially true for the small- to medium-sized enterprises in biotech. Bharat Biotech International has used numerous funding partnerships to subsidize its work on various drugs and vaccines and enhance its manufacturing capabilities. Obtaining funding from various government and nongovernmental organizations on a project-specific manner has been the company's central fundraising strategy and the firm has subsidized its R&D activities for several products (**Box 1**). Elsewhere, Shantha Biotechnics has capitalized on numerous public-private partnerships to help subsidize its research activities (**Box 3**), whereas GangaGen Biotechnologies has been able to raise some venture capital financing from a venture capital firm (ICF Ventures; Fairfax, VA, USA). Even Biocon, which has had considerable revenues in recent years through its sales of generic statins in the US market, has created two subsidiaries (Syngene and Clinigene) that generate revenues through contract research to help finance its own R&D activities. Transgene Biotek (**Box 4**) initially depended primarily on high-interest bank loans to develop the capabilities to produce its current product line.

Although the financial environment has improved over the past several years, developing an innovative health product remains a precarious venture for India's biotech entrepreneurs. Most executives attribute this to a risk-averse attitude among Indian banks and investors. As an official at Dr. Reddy's Laboratories explains,

Box 3 Case study: Bharat Biotech

Bharat Biotech (Hyderabad) started in 1996 and by 1998 had launched its recombinant Hep-B vaccine developed with its innovative HiMax technology. This technology significantly increased the yield of target proteins compared to existing methods at the time. This proprietary technology played a vital role in reducing production costs, allowing high protein recovery and making the vaccine affordable for millions more in India, with recent exports to Latin America. The company now enjoys significant manufacturing capabilities and has several products on the market and in its pipeline (**Table 1**).
Bharat claims to be the first vaccine manufacturer in a developing country to produce a proprietary product for a major multinational corporation (Wyeth's Hib vaccine). It was also the first company in India to receive a patent for a new biotherapeutic molecule (lysostaphin for use against staphylococcal infection), and to manufacture and market recombinant human epidermal growth factor and recombinant streptokinase. It is now in a position to invest in cash-poor biotech companies, including those from industrialized countries with promising technologies or to conduct good manufacturing practices (GMP) manufacturing, preclinical and clinical development of proprietary products.

Thus far, Bharat has invested ~$30 million in its facilities and operations and had revenues of >$9 million in 2004–2005, up nearly 14% from the previous year[16]. The firm has pursued a project-specific funding strategy, through which it has solicited and received funding from various sources. For example, the Council of Scientific and Industrial Research cofunded the development of lysostaphin through its New Millennium Indian Technology Leadership Initiative program, the Technology Development Board of India (TDB) partly financed the development of recombinant streptokinase, and the European Malaria Vaccine Initiative and the Bill and Melinda Gates Foundation are currently supporting the development of a malaria vaccine. In addition, Bharat was the first biotech firm in India to receive grants (>$11 million) from the Children's Vaccine Program and Malaria Vaccine Initiative (MVI) of Bill and Melinda Gates Foundation to finance its rotavirus and malaria vaccine programs. These funders are underwriting the company's efforts in pursuing high-risk projects, with the company itself shouldering only 25% of the development costs. In July 2001, Bharat partnered with MVI and the International Center for Genetic Engineering and Biotechnology (ICGEB, New Delhi) to develop a candidate malaria vaccine against *Plasmodium vivax*, the parasite responsible for most of the malaria cases in India. ICGEB provided the clone for protein expression and Bharat conducted the downstream processing and purified the protein. Therefore, Bharat benefited not only from the financial investment from MVI, but also from the technological knowledge transferred from ICGEB. Long-term investors in the company include the International Finance Corporation (Washington, DC US), Industrial Credit and Investment Corporation of India (Mumbai, India) and Venture and Industrial Development Bank of India (Mumbai, India), with some loans from the TDB.

"Early-stage funding for a company [that] wants to do pure research and go to the market six or seven years later does not exist. There is no money for such a business plan." Many feel that Indian fund managers and analysts have no culture of funding pure research–based companies and would not want to get involved in such a valuation exercise. Investments in domestic biotech firms remain small, although some local investors are beginning to move into the life sciences arena, including the Andhra Pradesh Industrial Development Corporation (Hyderabad) and Industrial Credit and Investment Corporation of India Ventures (Hyderabad). It is also of note that relatively few members of the Indian Venture Capital Association (New Delhi; http://www.indiavca.org/) identify biotech as an area of investment focus. International investment banks like Bank of America (New York) and Citibank (New York), however, are eyeing India's biotech sector, and some funds from abroad are beginning to trickle in, including investment from the International Finance Corporation (IFC; http://www.ifc.org/), the private sector arm of the World Bank Group (Geneva). Indian firms view foreign investors as sources not only of capital, but also technological partnerships and managerial expertise.

Small companies face the additional barrier that the relatively small funds they require to expand their businesses are often far less than the minimum thresholds set by international venture funds to reap an acceptable return on investment. Thus, small firms are often dependent on bank loans that would not disrupt their firm structure or overly dilute their majority shareholders' investments. A new financing model tailored to the needs of Indian small- to medium-sized enterprises is clearly needed to enable companies trying to develop innovative products to succeed. The government of India has responded to these needs by introducing several funding initiatives. For example, the Department of Science and Technology's Technology Development Board has invested over Rs 150 Crore (~$34 million) in 2004–2005 in health and medicine–related projects, the most for any sector of the Indian economy (http://www.dst.gov.in/). The Technology Development Board requires that their 'soft loans' be repaid with minimal interest (6%) upon successful completion of the project. Also, India's Council of Scientific and Industrial Research New Millennium Indian Technology Leadership Initiative program was set up to boost public-private partnerships between private companies, national research laboratories and academia. Thus far, this program has 37 ongoing projects covering diverse areas, with an aggregate expenditure of Rs. 220 Crore (~$50 million) over 2–3 years and involves 240 partners, with 175 in the public sector and 65 in the private sector (http://www.csir.res.in/). Because some firms we interviewed did point out that these programs helped boost their research programs by stimulating partnerships with domestic research institutes, they should be considered as models for future investment strategies by both public and private funding sources.

Another strategy that some domestic firms take is to form subsidiaries, often abroad, to help them access capital investments/expertise not available in India, facilitate knowledge transfer and expand into foreign markets. For example, Shantha Biotechnics has set up an independent subsidiary in San Diego (Shantha West) to develop human mAbs. Dr. Reddy's Labs, Transgene Biotek and Bharat Serums and Vaccines each have subsidiaries or research groups in the United States, focused on early R&D. Wockhardt's subsidiary, Wockhardt USA, deals with IP rights and regulatory affairs to facilitate introduction of their products into the North American markets. One of Avesthagen's subsidiaries, Avesthagen Biotherapeutics and Research, and Reliance Life Sciences's subsidiary, Reliance Clinical Services, are domestic expansions of the parent companies.

Barriers to development

During the course of this study, we identified several obstacles that are hindering development of Indian's nascent biotech sector. The seven major challenges to further growth are detailed below.

Multiple regulatory agencies delay commercialization. Many firms lamented the significant barriers presented by a poorly coordinated patchwork of different regulatory agencies in India. In dealing with several agencies, companies experience an approval process that causes significant confusion and delays the commercialization of health products. Firms also cited the lack of expertise in dealing with biologicals on the part of regulatory agencies as a significant burden to the growth of their sector. In their opinion, this contributes to the lack of international credibility of certificates from Indian regulatory agencies, which then forces some Indian firms to seek approval for their products from international regulatory bodies. Despite these limitations, however, many firms are optimistic that the situation will continue to improve with the sustained efforts and cooperation between the government of India and the domestic private sector.

Shortage of advanced training programs and scarcity of qualified personnel. Indian companies trying to improve their national and global competitiveness and enhance their in-house expertise and capabilities require access to a pool of highly trained personnel. Firms are finding that such a workforce of researchers trained in leading-edge biological methodology remains limited in India today. This is in part due to the migration of a large number of talented Indian PhD students and research scientists out of India, where they seek training and where greater research funds are available. Some firms also highlighted the need for a single agency to provide scientific guidelines, evaluation and advice to the country's pool of potential young talent for biotech research.

Public-private collaborations lack overall effectiveness. Despite the significant number of linkages between private and public institutions in India (a number of which have undoubtedly been fruitful), some firms expressed dissatisfaction in collaborating with Indian research institutes and universities because of "a difference in expectations" (**Table 3**). For example, one firm said that its previous experiences with Indian universities were disappointing because "what was promised was not delivered." India's draft copy of the National Biotechnology Development Strategy (Biotech Strategy), released in March 2005 (http://dbtindia.nic.in/biotechstrategy/BiotechStrategy.pdf), attempts to overcome this obstacle by supporting initiatives to promote public-private partnerships and stresses a shift in policy that supports cooperation (rather than competition) among science agencies, research institutions, universities and industry.

Few Indian academics show entrepreneurial ambition in biotech. Resident or returning Indian academic scientists founded only 4 of the 21 firms we contacted. Among these are Avesthagen, Strand Life Sciences and Bhat Bio-Tech India. Avesthagen was originally supported by grants from the Rockefeller Foundation and spun-off from the University of Agricultural Sciences (Bangalore) where the founder and CEO, Villoo Morawala-Patel was a professor. Strand Life Sciences was cofounded by chairman and CEO, Vijay Chandru, a professor at the Indian Institute of Science (Bangalore). And Bhat Bio-Tech India was founded by Shama Bhat, who returned to India after serving on the faculty of the University of Pennsylvania (Philadelphia) for over 10 years.

This trend has much to do with weak mechanisms for technology transfer between public research institutes and private firms, and weak policy structures that dissuade Indian academic scientists from pursuing entrepreneurial ventures. The draft Biotech Strategy lists several mechanisms to enable academic scientists to work in industry and undertake industry-oriented research, including improved lateral mobility between universities or research institutes and industry, the possibility of dual faculty and industry positions, joint salary support and institute innovation grants to allow academic researchers to develop their concepts into patentable technologies. Encouraging prominent scientists to work with or in biotech firms requires a change in practice and traditional attitudes, but is likely to improve knowledge and technology transfer across research groups. Successful implementation of such a policy will help facilitate the commercialization of health products for domestic needs, in much the same way that the Bayh-Dole Act regulating university-to-industry technology transfer has worked in the United States.

Dearth of financial resources and burdening bureaucracy. For the most part, Indian firms are looking to foreign sources to sustain funding for their research programs, because domestic funding from both public and private sources remains modest. Even when available, the minimum investment threshold set by international venture capitalists is often too high for many small- and medium-sized businesses. Domestic sources of funding, such as central and state government programs that

Box 4 Case study: Transgene Biotek

Transgene Biotek (TBL; Hyderabad) started out as a strictly diagnostics R&D and manufacturing company in 1991 and had its initial public offering on the Bombay Stock Exchange in 1992. It currently has a number of products and technologies ready to be outlicensed (**Table 1**) or launched into commercial markets.

TBL's business model relies on technological transfer from other organizations. The company aims to acquire or in-license early-stage technologies with high market potential from research scientists, universities and small research institutes. It then uses in-house expertise and assistance from strategic collaborators to advance these technologies through process improvement and optimization, and preclinical animal studies. The firm has recently completed phase 3 human clinical trials of a quadrivalent Maningococcal vaccine developed in collaboration with JN International Medical (Omaha, NE US). TBL also has several ongoing collaborative projects with partners in India and the United States for some of its other products (**Table 4** and **5**).

Today, TBL generates revenues primarily through out-licensing novel technologies through strategic marketing partnerships for several products. The company's growth strategy is to bolster its product pipeline by reinvesting revenues generated through contract research into innovative products. It serves its clients by performing preclinical and early-stage clinical trials in India for the purpose of providing early safety and efficacy data for new drug candidates. Early data is meant to help lower the risk for later phase (and more expensive) investments in drug development by companies and researchers from advanced industrialized countries. The technological know-how and revenues acquired by providing contract services helps the company to bolster its own product pipelines.

In 1994–1995, TBL acquired the technology to make Hep-B vaccine and went through significant difficulties in securing capital in the years that followed, with high-interest bank loans (at 21%) being their primary source of financing. The company has since sold its recombinant Hep-B vaccine technology and invested a cumulative sum of ~$4.5 million thus far in shaping itself into a vaccines and biotherapeutics company, with additional capabilities in agricultural biotech applications, for example, for producing recombinant proteins for use in human therapy.

Biocon headquarters, Bangalore.

provide grants for R&D spending or soft loans to promote product commercialization, have been exploited by some firms. For instance, LifeCare Innovations (Gurgaon) received several grants from the Department of Science and Technology, and Bhat Bio-Tech received initial loans from the Karnataka State Industrial Investment Development Corporation. Even so, other firms have chosen not to apply for government funding because they find the administrative logistics too tedious and time consuming.

The government of India is proactively introducing sustained funding and fiscal initiatives to facilitate the growth of its biotech sector. For example, the Department of Biotechnology's budget increased from ~$30 million in 1999 to nearly $120 million in 2005 and the government has promised to nearly double its science budget from 1.1% of its gross domestic product in 2005 to 2% by 2007 (refs. 6,7). Fiscal incentives include relaxed price controls for drugs, removal of foreign ownership limits, subsidies on capital expenses and tax holidays for R&D spending[8]. For example, several firms (including Syngene, SIRO Clinpharm, Bhat Bio-Tech India, Serum Institute of India and Wockhardt) have declared themselves 100% export-oriented units, a designation that allows them to claim back custom duties on imported materials. Because a large majority of equipment necessary for a research facility must be imported, and custom duties can be as high as 45% on certain goods, this designation can mean significant cost savings. The draft Biotech Strategy also aims to create a favorable and enabling environment for enterprise creation and private sector development, including financial and problem-solving support for both early-stage innovative research and later-stage product development.

Lack of national prioritization diverts focus from domestic health needs. As Indian firms become more successful, they face a growing dilemma between doing innovative R&D and delivering affordable quality products at home. Strong competition among multiple domestic manufacturers is driving down market prices and reducing profit margins. One executive asks the question, "How do you do innovative R&D when your vaccine costs 10 rupees per dose?" Others felt that innovation and affordability are not mutually exclusive, and cited the use of tiered pricing schemes to maximize profits abroad while maintaining affordability at home.

Indeed, many of the firms recognize that investing in products that address domestic health needs is a business opportunity. That said, even if they feel their companies have the capabilities to develop these products, they also lament the lack of political will and of sufficient research funding to support such research programs adequately, particularly for affordable health products for India's poorest populations. Many interviewees suggested that they would be more committed to providing innovative products at a low cost domestically if additional funds for developing such products were made available by the government of India, global health organizations, the WHO or international investors. The draft Biotech Strategy appears to emphasize the importance of mobilizing domestic biotech firms to address prioritized national health needs by pointing out that both 'public good' and 'for profit' research should become mutually reinforcing.

The government of India has made available some funding through the Department of Science and Technology for companies to work on projects relevant to local diseases, like leprosy and tuberculosis. LifeCare Innovations, for example, received funding from the Department of Science and Technology to develop a new drug delivery system for a tuberculosis drug, and found the government to be receptive to funding such projects. Even so, many of the other firms interviewed were unaware of any government-sponsored programs to support the commercialization of products focused on local health needs. This problem should be somewhat alleviated now that the Department of Biotechnology is increasingly advertising its programs in local newspapers, and in June last year, began publishing a widely distributed newsletter called *Biotech News* that announces and explains its funding schemes.

High costs associated with domestic distribution. Indian firms use both domestic and international networks to market and distribute their products. Many Indian firms have domestic sales forces, but due to the high cost of distribution in rural areas, several vaccine manufacturers also rely on the government of India's expanded program on immunization for distribution of their products. Innovative approaches are needed to help reduce the high distribution costs associated with delivering health products across India and increasing access, especially in rural areas.

Indian Immunologicals, a firm that is wholly owned by the National Dairy Development Board, uses an innovative distribution network of franchise clinics to ensure that its affordable and high-quality human rabies vaccine reaches rural villages. Using refrigerated vehicles, Indian Immunologicals delivers this vaccine directly from its manufacturing facilities to a network of 1,500 rural clinics equipped with refrigerators and managed by Indian Immunologicals' network of local general practitioners and pediatricians who provide initial and follow-up wound care to patients affected by dog bites. The company hopes to broaden and expand this extensive network to deliver additional vaccines to other rural areas.

Other Indian firms are pursuing increased market share for exports, and have signed

product distribution contracts with international partners to do so. For example, Spectrum Pharmaceuticals (Irvine, CA, USA) is distributing Shantha Biotechnics' Hep-B vaccine, United Bioinformatica (UBI; Calgary, Alberta, Canada) is distributing Strand Life Sciences' Acuris bioinformatics product, and UCB South Africa (Johannesburg) is distributing Bhat Bio-Tech India's (Bangalore) HIV diagnostic.

Concluding remarks

India has demonstrated that a developing country can be successful in emerging high-technology fields, such as information technology and biotech. Government policies and support, and the expertise and efficiencies of the private sector, are each important contributors to the development of these emerging fields. This analysis of India's private health biotech sector reveals that the creativity and astute management of the firms themselves are particularly crucial elements of success for India's health innovation system. As such, these firms provide several valuable lessons for other developing countries that wish to strengthen their health innovation systems, and for individual companies that wish to develop or enhance their capacity in biotech. They also have prompted a set of recommendations for the Indian biotech sector as a whole (**Box 5**).

The first lesson from the India case is that many local firms started small with one or a few familiar products and/or services to generate early revenues, and leveraged early success for later growth. For example, several Indian firms started by entering the vaccine sector for which there is significant expertise in the country and limited competition from abroad. These firms continue to leverage revenues from the sale of these vaccines to develop more innovative vaccines, therapeutics and technologies. Local firms also accelerated their foray into biotech by developing more efficient fermentation processes, for example, which allowed them to take advantage of complementary technologies as well as generate early revenues.

Second, Indian health biotech firms have been resourceful in exploring various financing opportunities from both domestic and international sources (**Boxes 1–4**). Contrary to the common practice in the advanced industrialized countries where biotech firms tend to raise financing by offering equity in their firms, and necessitated by the dearth of domestic venture capital available, Indian companies have often grown without having to surrender much equity. Instead, they have grown through first adopting a hybrid business model—where early revenues are reinvested to expand product and/or service portfolios—and second, relying on project-specific financing from external governmental and nongovernmental agencies.

Third, successful firms have been very proactive in establishing and maintaining collaborations and partnerships with both public and private organizations in India and abroad (**Tables 4** and **5**). Indian firms are also establishing a global presence through joint ventures with foreign firms or by setting up their own subsidiaries abroad (**Table 2**). Regardless of their form, these linkages are mutually beneficial relationships that can serve to transfer technology and knowledge bi-directionally between the industrialized and developing countries.

Fourth, Indian firms are aiming to become more competitive by patenting their products and technologies, and they are doing so on a global basis (**Table 6**). On a national level, India has been able to capitalize on domestic policies that emphasized process patents over product patents to build a pharmaceutical industry with strong capabilities in generics manufacturing. This approach may be useful to consider especially for less developed countries for which the WTO's TRIPS agreement allows exemptions on pharmaceutical patent protection until the year 2016 (http://www.wto.org).

Lastly, successful Indian firms have been able to establish and maintain favorable reputations internationally. Several of the firms we interviewed employed senior managers who spent several years training and working abroad. Many cited this international experience and confidence as instrumental in forging initial partnering relationships, the success of which has led to subsequent opportunities. The value of trust in building and maintaining international credibility is quite important for a young biotech firm that is highly dependent on collaborations[9], particularly when that firm hails from an emerging country that is still developing its innovative capacity.

Given that the Indian biotech sector has developed along these lines, our study also has identified several areas that warrant further research and study to ensure further development of the industry.

Human resources. A common perception that has not been adequately surveyed is that India is generally strong in chemistry and process development but short of biological investigators. The scientific labor pool needs to be investigated further to identify gaps in expertise, more precisely, to guide public policy and national investment in the biological sciences. In addition, as this article demonstrates, R&D alliances between Indian and Western companies have just begun and may be affected by assumptions—correct or incorrect—about the expertise and competence of the workers at Indian firms.

Recently, major Western pharmaceutical firms, such as Novartis, have created their own research facilities in India. This trend, including the subsequent need for domestic firms to provide competitive salaries to retain talented personnel, raises the question of whether there will be an impact on the labor pool and the research strategies of domestic pharmaceutical and biotech companies. For example, the increased costs incurred by local companies to provide competitive salaries to retain talented personnel may put further pressure on margins of domestic products, and may push companies to shift focus to higher-margin products and services for Western markets.

Box 5 Recommendations for biotech development in India

On the basis of our study of India's private health biotech companies, we offer below six recommendations to encourage continued development of the sector.

- Harmonize the pharmaceutical regulatory system into one regulatory agency and ensure adequate training for regulatory personnel.
- Increase training programs in advanced biotech and form a single agency to provide science mentoring and provide scientific guidelines.
- Ensure translation of initiatives in the draft Biotech Strategy into policies that increase effective collaborations between public and private institutions and encourage academic scientists to pursue entrepreneurial ventures to commercialize research.
- Create a favorable and enabling financial environment for enterprise creation and private sector development, including support of early-stage research and product development.
- Identify national priorities for public health and use a targeted funding approach to ensure development of products and services that address local health needs.
- Improve public health infrastructure and/or give incentives to private firms to develop innovative distribution strategies.

Table 6 IP portfolios/marketing rights for companies interviewed[a]

Company name	Information on significant patents
Avestha Gengraine Technologies	Currently has ~60 patent applications, 22 of which are filed under Patent Cooperation Treaty (PCT), including two rice patents filed in the US. Range of technologies include: molecular markers, transgenic plants, novel proteins and methodologies. A patent for 'pearl Millet' has already been granted in South Africa and Australia
Bharat Biotech International	Approximately 20 patents overall. (A novel process for preparation and purification of hepatitis-B surface protein (HIMAX) in India; Expression of recombinant streptokinase in US, Expression of recombinant mature lysostaphin-BH005; works against MRSA, Vero adaptation of rotavirus vaccines, *S. aureus* vaccine)
Bharat Serum and Vaccines	Patents granted for novel formulations in US (amphotericin emulsion, lipid free propofol), in Europe (Ifosfamide with Mesna, amphoptericin B lipid complex). Other patents on these and other drug delivery systems at various stages in 40–70 countries
Bhat Bio-Tech India	Currently applying for a few patents, both in India and abroad, for tri-line HIV test and combo-test for HIV and HCV
Biocon	Patent portfolio of over 300 patents including ~15 US patents including some for fermentation devices and various processes for production of certain therapeutics and over 100 innovation patent applications are at various phases. Its recent acquisition of Nobex gave Biocon IP rights to IN-105 (an oral insulin), BN-054 (an oral peptide for cardiovascular disease), Oratonin (an oral calcitonin in phase 1 trials for osteoporosis), Oral PTH (parathyroid hormone) and APAZA (in phase 1/2 trials for inflammatory bowel disease)
GangaGen Biotechnologies	Has two US patents: One for a genetically modified lysogenic phage (to be used as an anti-bacterial agent) and another on utilizing phages to develop whole cell vaccines
Indian Immunologicals	Applied for novel combination of rabies combination vaccine (made up of conventional rabies vaccine and a DNA plasmid) in a number of countries and has already been granted in South Africa
Nicholas Piramal India	A portfolio of 36 patents and 173 patent applications at various stages
Panacea Biotec	Seven products patented in the US and 4 in Canada and numerous patent applications in the pipeline including 18 PCT applications. The exclusive products based on patented drug delivery system include: Xeed (for optimum bioavailability of rifampicin), nimulid safeinject (parenteral formulation of nimesulide), panimun bioral (cyclosporine modified formulation), ThankGod (*Euphorbia prostrata* extract for management of hemorrhoids), Nimulid MD (nimesulide tablets), Willgo (nimesulide formulation), Nimulid Transgel (nimesulide transdermal gel), Nimcet (combination of nimesulide + cetrizine) and ODPEP (pantaprosole+domeperidone). The company has filed 316 applications worldwide and 129 in India
Reliance Life Sciences	Currently has ~130 patent applications in different stages of approval
Shantha Biotechnics	Product patent portfolio with Shantha West, for monoclonal antibodies. One US patent granted and four more at various stages. Seven patents under review in India and three have been granted. Patent activities span hepatitis B process patents, insulin process patent, antibodies that recognize hyperproliferative cells and methods of making and using these cells
Strand Life Sciences	Mainly protects products by keeping source code private, but has also filed a few provisional patents
Transgene Biotek	US patent on oral delivery platform for insulin, and in the process of filing many more patents
Wockhardt	150 patent applications submitted so far including three in pharmaceutical biotech covering their protein expression systems

[a]Patents may include and are not limited to: biological and pharmaceutical products, development processes, drug delivery platforms, and others.

Intellectual property. In light of the implementation of TRIPS in India as of January 2005, there needs to be business-oriented research on the effect of the new IP regime on the industry, including changes in strategy, the impact on cash resources, and effects on the formation and management of alliances. Such research would benefit firms that are expanding their efforts on development of proprietary products, and have both public policy and capitalization implications.

Capital resources. Assessment of biotech entrepreneurship, in terms of numbers and degree of talent, is essential to answer questions related to future investment by venture capitalists, the confidence needed by prospective partners in strategic alliances and access to Indian and foreign capital markets. Findings will suggest programs for Indian business schools and industry-related group training programs.

The availability of capital for companies developing commercial products that have not yet gone to market may remain a difficulty for Indian firms. Further analysis of the causes and remedies is a fertile ground for investigation. In addition, study of the due diligence concerns of the investment community might serve as a guide to companies as they formulate strategies and build their management and scientific teams.

Many major Indian pharmaceutical companies are actively accessing the capital markets to raise cash for the acquisition of companies and products. In the United States, the biotech industry has relied on financing from major corporations in the form of payments for collaborative research, and eventually through product royalties. This begs the question to what degree will further capitalization of the major Indian pharmaceutical companies finance the Indian biotech sector?

Market forces. To compete globally, Indian companies are likely to accelerate the development of products for sale in US and European markets, particularly the biogenerics for which they have developed significant manufacturing capacity. Foundations and nongovernment organizations, which have historically supported and promoted development of essential medicines and vaccines at affordable prices, have expressed concern that Indian firms, which have played a critical role in meeting the needs of the Indian population, will largely abandon that contribution. This may or may not prove to be the case and should be studied further. If it is the case, additional research will be needed to suggest approaches to reconcile the differences between commercial and public health needs.

The nature of competition will necessarily change from solely price-based to competition on a broader range of factors, such as product positioning, branding, promotion and aggressive contracts with Indian healthcare providers. Monitoring how these changes influence strategy and capitalization is fundamental to determining India's future role in the creation and production of products for its own population and the needs of developing countries.

The system of Indian private and public healthcare is rapidly evolving and new insurance programs have begun to emerge. Over time, changes in delivery systems will drive fundamental shifts in product development and marketing strategies. This evolution will affect both domestic companies and foreign companies entering the market. The interplay of healthcare policies and commercial strategy

might influence company strategy related to the research questions posed above.

Addressing local health needs. Developing nations strive to provide health products and technologies to meet their own populations' needs. India's experiences highlight several key influences necessary to strengthen national health innovation systems and to promote the innovative capacity of domestic health biotech firms to address local needs. These include the following: training and education in advanced scientific methods; effective collaboration between public and private research groups, streamlined regulatory procedures and sustained and adequate funding for development of prioritized health products.

India's health system is in the midst of being hit with a 'double burden' of communicable and noncommunicable diseases, as basic care improves and the country's middle class grows. In 2003, 5.1 million Indians were living with HIV/AIDS, over 3 million had tuberculosis and 1.8 million had malaria[10–12]. Approximately 32 million Indians were diabetic in 2000, a number that is expected to reach 80 million by 2030 (ref. 13). The WHO predicts that by 2015 nearly twice as many deaths in all ages in India will be due to chronic diseases than to communicable diseases, maternal and prenatal conditions, and nutritional deficiencies combined[14].

Historically, Indian companies have been the principal providers of medicines and vaccines for the Indian population, enabled by domestic talent and patent laws that protected processes but not products. Inevitably, local competition was reduced to pricing wars that eroded the capacity of established companies to self-funded proprietary R&D, and discouraged the formation and capitalization of innovative new biotech companies.

Indian pharmaceutical companies have demonstrated a competence and capacity to produce world-class quality pharmaceuticals. Thus, the prospect of selling proprietary products in international markets has had an understandable allure. If Indian companies allocate resources to meet the demands of competing in these markets, they may devote less time to domestic markets, and possibly to the medical needs of less developed countries. India needs to take steps to avert this outcome.

The government of India might consider identifying a few priority disease areas, and create a dedicated fund for the commercialization of products related to these diseases. Such a 'push' mechanism demonstrates the government's commitment to enlisting the talents of its domestic biotech sector in addressing issues of national priority, and is similar to the CSIR New Millennium Indian Technology Leadership Initiative program in that regard. The availability of significant research funds essentially lowers the risk for the projects for the private companies and motivates them to invest internal resources. For example, Bharat Biotech International is codeveloping a rotavirus vaccine and a malaria vaccine with funding from various global health programs. In the course of our study interview, Krishna Ella, the company's founder and chairman, explained that the company never would have initiated these projects on its own because it did not have the expertise or the financial means for doing so. The funds from the global health programs, however, made the projects much more attractive to the company. "So we take only 25% risk in that. We're only putting in 25% of the funding, 75% is coming from them. And we don't mind losing 25% because if we hit, we hit [the] big one!"

The high costs associated with distribution to rural areas, where public health infrastructure is weak, effectively deter local companies from developing products for regional diseases and should not be underestimated. Many firms admitted they did not see the point in committing limited resources to commercializing products that would ultimately never reach patients. In addition to improving delivery infrastructure, the government of India can devise national and regional procurement plans to encourage domestic private sector involvement in this area. Similarly, governments could offer private firms incentives or rewards for developing their own innovative distribution mechanisms, like the franchise clinic distribution model of Indian Immunologicals, described above.

There is a sense of responsibility, however, among some Indian firms for developing products that are affordable and accessible to domestic and less-developed markets. "I think if anybody has to address regional diseases, it's us. We don't expect companies from the West to do that because it may not make commercial sense for them to do so," noted one interviewee. Kiran Mazumdar-Shaw, chairman and managing director of Biocon puts it this way: "Today there is no point to finding a wonder drug….I think ultimately companies will have to realize that unless they can create large market opportunities, fairly reasonable and affordable pricing, these products are not going to find their way to the patients who need them. I think that is the challenge."

Note: Supplementary information is available on the Nature Biotechnology website.

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COMPETING INTERESTS STATEMENT

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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