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India's Role in Global Health R&D

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Acronyms

All India Institute of Medical Sciences	AIIMS
antiretroviral	ARV
Active Pharmaceutical Ingredient	API
Biotechnology Industry Partnership Programme	BIPP
Biotechnology Industry Research Assistance Council	BIRAC
Centers for Disease Control and Prevention	CDC
contract research organization	CRO
Council of Scientific and Industrial Research	CSIR
Department of Biotechnology	DBT
Department of Pharmaceuticals	DPT
Department of Scientific and Industrial Research	DSIR
Department of Science and Technology	DST
Drug Controller General of India	DCGI
Drugs for Neglected Diseases Initiative	DNDi
Drugs and Pharmaceutical Research Programme	DPRP
Expanded Programme on Immunization	EPI
Food and Drug Administration	FDA
Foundation for Innovative New Diagnostics	FIND
GlaxoSmithKline	GSK
Global Alliance for Vaccines and Immunization	GAVI
Global Funding of Innovation for Neglected Diseases	G-FINDER
Government of India	GOI
hepatitis B	Hep B
Haemophilus influenza type B	Hib
human papillomavirus	HPV

Indian Council of Medical Research	ICMR
intellectual property	IP
International Center for Genetic Engineering and Biotechnology	ICGEB
International Finance Corporation	IFC
International Vaccine Institute	IVI
Medicines for Malaria Venture	MMV
Meningitis Vaccine Project	MVP
multinational corporation	MNC
National Institutes of Health	NIH
new chemical entity	NCE
New Millennium Indian Technology Leadership Initiative	NMITLI
Organization for Economic Cooperation and Development	OECD
Pan American Health Organization	PAHO
Program for Appropriate Technology in Health	PATH
private equity	PE
product development partnership	PDP
research and development	R&D
Small Business Innovation Research Initiative	SBIRI
Special Programme for Research and Training in Tropical Diseases	TDR
Technology Development Board	TDB
Trade Related Aspects of Intellectual Property Rights	TRIPS
United Nations	UN
Universal Immunization Program	UIP
venture capital	VC
World Health Organization	WHO

EXECUTIVE SUMMARY

Despite India's rapid economic growth and growing technological prowess, it continues to suffer from widespread poverty and a heavy burden of infectious disease, including high rates of tuberculosis, malaria, and other so-called neglected diseases.

To reduce this burden, India will have to strengthen its health system, especially for the poor, and increase access to existing medicines. But in India, as in other developing countries, new health technologies—such as affordable and locally adapted drugs, vaccines, and diagnostics—can also make a big contribution to combating disease. For some important diseases, there are currently no effective drugs or vaccines, whereas for others, existing technologies are too expensive, require infrastructure that is not broadly available, or are ill suited in other ways to local needs. For example, there are no vaccines against malaria or dengue fever and no cheap and accurate point-of-care tests for tuberculosis.

India already manufacturers most of the drugs, vaccines, and diagnostic tests it uses and has established itself as an important supplier of affordable drugs and vaccines to other developing countries. In most cases, these products were first developed by scientists and companies in high-income countries, but India's capacity for innovation—and that of other rapidly developing countries, such as China and Brazil—is growing. To what extent can India contribute to the development of new health technologies to meet the needs of its own population, as well as those of other low- and middle-income countries? Are for-profit Indian firms more likely to invest in products for neglected diseases than are the established multinational companies based in high-income countries? What are the main obstacles to neglected disease research and development (R&D) in India, and how might they be overcome?

This report, based on interviews with policymakers, industry executives, and Indian and international experts, explores these questions. It surveys the landscape of neglected diseases R&D in India, assesses strengths and weaknesses, and makes recommendations for both the government of India and international organizations interested in the development of new technologies to combat neglected disease in developing countries.

Overview of the Indian Health Innovation System

Biomedical innovation requires scientists, engineers, and managers with the right mix of skills; publicly supported research with strong links to industry; financing for product development; access to technology; rigorous but supportive regulation; functioning infrastructure; and, of course, markets for products. These elements are in place in India to varying degrees, but important gaps remain.

Although India has quite a strong tradition of public-sector scientific research, links to industry are weak, with the result that relatively few technologies developed by public-sector researchers are successfully commercialized (some important exceptions are noted below). For their part, the private Indian

pharmaceutical and biotech industries are thriving, but they have, at least until recently, focused mostly on production of generic drugs or versions of existing vaccines and diagnostics rather than on innovation.

R&D financing is another important constraint, as there is still little private equity or venture capital investment in early-stage biomedical projects in India. New government programs providing grants and soft loans to industry have helped fill this gap and are particularly important for neglected disease projects, which have little commercial potential. International funding has been important for late-stage clinical trials of several vaccines.

One barrier to R&D often cited by industry executives is a regulatory system that is poorly equipped to oversee the development and approval of new (as opposed to generic) products. Regulatory obstacles are particularly severe for products based on genetic engineering and biotechnology, which require review by several different agencies. According to firms, regulators often lack familiarity with the relevant science.

The pull of public-sector markets as an incentive for product development has been limited by low prices; slow adoption of new products, especially vaccines; and lack of clear signals on new technology priorities for future procurement.

The Indian government has launched a range of initiatives to address these weaknesses in the biomedical innovation system, but in most cases it is too early to assess their impact.

Vaccines

India's vaccine R&D capacity is growing and it is now in a position to make important contributions to the development of needed new vaccines.

The Indian vaccine industry began as a network of state-owned manufacturers supplying basic childhood vaccines to the national immunization program. In recent decades, a number of privately owned firms have grown rapidly, developed the capacity to produce more sophisticated vaccines, and become important suppliers to other low- and middle-income countries, in particular through UNICEF and the Pan American Health Organization. Total revenues of India's vaccine companies have reached about $500 million and are projected to grow at more than 10 percent per year. Both the Indian market and Indian vaccine companies remain small in comparison to U.S. and European markets and to the largest multinational firms—the largest international vaccine manufacturer, GlaxoSmithKline, alone earned more than $6 billion from its vaccines business in 2010.

Exports account for more than 40 percent of the Indian vaccine industry's sales. Unlike Indian drug firms, however, the nation's vaccine companies have not yet gained access to the U.S. and European markets and remain largely focused on public-sector and UN markets in low- and middle-income countries.

In R&D, the leading firms have moved from process development and incremental innovation in combinations and formulations to the development of new vaccines and have developed expertise in recombinant technology. Across the industry, a dozen or so new vaccines—against rotavirus, Japanese encephalitis, typhoid fever, malaria, rabies, and influenza—are in clinical development. Many more projects are at earlier stages, including efforts on dengue, chikungunya, and cholera.

Important limitations remain, however. No Indian firm has ever developed a truly new, first-in-class vaccine: the industry's current products, as well as most of the vaccines in its R&D portfolios, are based to varying degrees on licensed vaccines. Indian industry has little experience with the large-scale community-based clinical trials necessary to prove efficacy of new vaccines, and it remains relatively weak in vaccine discovery. And although there are promising vaccine research projects underway at a few public research institutions, ties between public-sector researchers and the vaccine industry remain weak, and companies have, in most cases, relied on technology acquired from abroad. A notable exception is the rotavirus vaccine developed at the All India Institute of Medical Sciences and now in advanced clinical trials with Bharat Biotech International.

Despite these constraints, the growing R&D capacity of Indian vaccine companies and their continued focus on developing-country markets mean there is considerable potential for India to contribute to the development of needed new vaccines for low- and middle-income countries, including India. One of the most important roles that Indian firms can play, as they have in the past, is to bring to market new versions of existing vaccines of global health importance, such as rotavirus, pneumococcal conjugate, and human papillomavirus vaccines, driving down prices and ensuring supply to the Global Alliance for Vaccines and Immunization and middle-income countries. Having an Indian supplier also makes it more likely that India will incorporate these vaccines into its public-sector immunization program. Such "follow-on" vaccines, unlike generic drugs, require considerable R&D investment and independent clinical testing and are thus within the scope of this report. India can also help develop new and adapted vaccines against some other neglected diseases, as illustrated by Serum Institute of India's meningitis A vaccine for Africa.

Continued financial and technical support from international partners, as well as further financial support from the Indian government, will be important to achieving these goals. These partnerships can help overcome remaining capacity constraints and facilitate access to technology, as well as make development of vaccines with small or modest markets commercially viable. Although Indian firms are willing to pursue products with markets that would be too small to interest the big multinationals, they cannot afford to develop vaccines for the most neglected diseases—chikungunya or typhoid fever, for example—without substantial subsidy. The prospect of donor-subsidized sales through GAVI is a powerful inducement for these firms, but only a subset of needed vaccines are included in GAVI's portfolio. Some up-front subsidy is also necessary for vaccines such as rotavirus, despite the GAVI market, as most Indian firms do not have access to the capital to finance the needed large clinical trials. This report includes an in depth-look at rotavirus vaccine development in India.

Drugs

Unlike the vaccine companies, Indian drug firms show little interest in developing new drugs against neglected diseases, although they remain crucial suppliers of affordable medicines to India and to other low- and middle-income countries.

The Indian drug industry is considered a success story for Indian industrial policy. Sheltered by India's decision in the 1970's not to award product patents on drugs and to restrict foreign participation in the industry, Indian companies developed expertise in drug process development and low-cost production, laying the groundwork for a thriving generic drug industry that has continued to expand since the implementation of product patents in 2005. Several Indian firms have won approval for their drugs in the United States and Europe, and India is now the world's fourth-largest supplier of generic drugs. The pharmaceutical industry brings in about $20 billion a year, with more than $8 billion coming from exports.

A widely shared expectation that the Indian drug industry would shift toward a more R&D-based model after India changed its patent laws in 2001 has not been fully met, however. Although the leading firms have increased R&D spending in the past decade, levels of investment remain relatively low, averaging 8 percent of sales compared with 10 to 20 percent of much larger sales for the big multinationals. Moreover, most firms have drawn back from new drug development, focusing instead on R&D related to their thriving generic businesses. At the same time, a contract research industry focused primarily on process and analytical chemistry and on clinical trials had grown rapidly in recent years.

Lucrative international markets for generic drugs promise quick returns for shareholders, and there is little incentive for Indian firms, most of which are publicly traded, to refocus their efforts on neglected diseases. In addition, their skills in drug discovery are limited, and the R&D efforts of both the large generic producers and the contract research organizations are focused primarily on products with global markets. There are some notable exceptions—for example, Ranbaxy Laboratories recently launched a

new malaria drug initially developed in collaboration with the Medicines for Malaria Venture.

Although it seems unlikely that Indian drug firms will develop new drugs for neglected diseases on a commercial basis, even with Indian government or international subsidy, these firms are well-placed to develop needed new formulations and combinations of existing drugs. For example, Indian firms are continuing to take the lead in developing new fixed-dose combinations of HIV drugs. Moreover, Indian firms can contribute to international R&D initiatives on a fee-for-service basis in aspects of R&D where they have expertise and enjoy cost advantages, for example in chemical synthesis. In fact, an Indian contract research organization was recently named a preferred provider to a consortium of global health product development partnerships.

Public-sector institutes, in particular the Central Drug Research Institute, are pursuing a range of drug R&D projects for both infectious and noncommunicable diseases. Some projects for neglected diseases are now being conducted on open-source basis, but it is not yet clear what form partnerships with industry will take for these projects or whether this will yield new products.

Diagnostics

There is considerable potential for India to contribute quickly to the development of new locally adapted diagnostics for both infectious and noncommunicable diseases.

India's in vitro diagnostic industry comprises a set of established firms with broad portfolios of tests based on established technologies, including serological tests for a range of infectious diseases, as well as a handful of more innovative small companies. Although the R&D capacity of India's test developers, like that of its drug and vaccine industries, still lags well behind international leaders, these firms have the expertise to bring to market tests based on established platforms relatively cheaply when appropriate biomarkers are available. A few Indian firms may also be able, with technical and financial assistance, to develop new diagnostic platforms that could be more affordable and require less infrastructure than existing products. An intriguing case is the new point-of-care nucleic amplification system being developed by Bigtec Labs in collaboration with the Tulip Group.

Diagnostics are a particularly promising area for India firms because the cost and time required to develop a new in vitro test is in general substantially lower than that of bringing a new drug or vaccine to market. This, in turn, lowers financial barriers and makes products for relatively small markets in developing countries commercially viable.

Another positive factor for diagnostics development in India is that there appears to be more productive collaboration between the public-sector laboratories and industry. A number of tests initially developed in the public sector have been successfully commercialized, including dengue and hepatitis C tests developed at the International Center for Genetic Engineering and Biotechnology in New Delhi, and many institutes are working on diagnostics for neglected diseases. Lack of clarity about regulatory standards and processes for assessing new diagnostic tests, in India and at the international level, is an important barrier to diagnostic R&D in India.

Although this report focuses on infectious diseases, managing the growing burden of noncommunicable diseases in India and other low- and middle-income countries will also require a range of more affordable new diagnostics, including point-of-care tests requiring little training or infrastructure. Working together and with help from government and international technical partners, India's researchers and diagnostic companies should be in a good position to develop and supply many of these tests.

This report also includes a short case study of tuberculosis diagnostics development in India.

Conclusions and Recommendations

This analysis conveys a mixed picture. On one hand, the capacity of Indian firms—and of the Indian

biomedical system as a whole—to create and bring to market new health technologies is still limited in important ways. On the other hand, there are already important areas of strength, and, in general, capacity is growing. Indian firms require subsidy of some kind to work on products with very small markets, such as leishmaniasis or typhoid fever, but there does seem to be a class of useful neglected disease products that these firms see as commercially viable.

Crucially, there are big differences across product types and stages of R&D. The greatest opportunities for neglected disease R&D are probably in vaccines and diagnostics. Although firms in these areas are smaller than the leading drug manufacturers, they are investing in R&D and are interested in at least some neglected disease products. The drug firms, in contrast, are primarily focused on building their generic drug businesses and on global markets.

Indian companies are most able to contribute in three ways: by developing more affordable or locally adapted versions of existing products; by bringing to market some new products to which technological barriers are not too high; and by participating in specific aspects of international product development initiatives in areas where they have a cost or other advantage.

The Indian government and international partners can help strengthen Indian health R&D capacity and ensure that this capacity is used to meet public health needs in India and other developing countries through action in four areas.

First, both the government and international donors should expand financing for promising neglected disease product development projects, including for late-stage clinical trials and for new, innovation-driven firms. Joint financing schemes, such as the existing collaboration between the Department of Biotechnology and the Wellcome Trust, are a promising way to channel international funding for R&D.

Second, international partnerships that provide technical assistance and access to technology should also be expanded. Although bilateral partnerships like the Program for Appropriate Technology in Health's assistance to Bharat's rotavirus project have been very useful, access to some technologies and relevant know-how could be shared on a more open, multilateral basis. The "technology hub" for influenza vaccines created by the World Health Organization (WHO), which made production know-how available to developing country manufacturers, is one possible model. In addition, shared resources, such as sample banks and intellectual property landscapes in key technology areas, could accelerate product development.

Third, both the Indian government and international health donors and procurement agencies could give neglected disease product development a big boost by sending clearer signals about the products they wish to buy, technical standards that will have to be met, and approval and procurement procedures. This is particularly true for diagnostics, where product needs and assessment processes have not been well defined either in India or by relevant international agencies and donors. Greater coordination between the public health and research-funding agencies of the Indian government is also important.

Fourth, the Indian system for regulating pharmaceutical and biotechnology R&D needs to be streamlined, and systems and capacity for evaluating new technologies strengthened. Although some arms of government recognize this need, and promising initiatives are underway, progress has been slow so far. At the same time, international systems for assessing and recommending products, especially WHO's prequalification program for diagnostics, need to be expanded so they can handle more products more rapidly.

The analysis presented here is broadly consistent with prevailing views of leading Indian experts and policymakers, as well as international experts, and many of these recommendations would build on existing initiatives and reform proposals. The authors hope that this report can give added impetus to these efforts.

CHAPTER 1
INTRODUCTION

1

India has established itself as a leading producer of low-cost drugs, vaccines, and diagnostics and has played a crucial role in bringing a range of affordable medicines to developing countries.

Indian manufacturers now produce 80 percent of the drugs used in donor-supported AIDS treatment programs[1] and are important suppliers of malaria drugs as well. Companies in India sell rapid tests for HIV and malaria to programs in Africa and elsewhere, while Serum Institute of India alone supplies vaccines used in 140 countries.[2]

However, India and other so-called innovative developing countries, such as China and Brazil, aspire to be more than producers of cheap medicines: these countries have a growing ability to develop new products, and both governments and firms are investing in strengthening pharmaceutical and biotechnology research and development.[3] This could be an important opportunity for global health, as these countries may be able to contribute to the development of new health technologies needed not only by their own populations but also by the poor in other parts of the developing world.[4]

The need for these products is great: new or adapted drugs, vaccines, and diagnostics are needed for malaria, tuberculosis, and a range of neglected tropical diseases, as well as for noncommunicable diseases (new product needs in each product area are reviewed in Sections 3 through 5 of this report).

Most international approaches to filling these gaps have relied primarily on researchers and product developers—and funders—in Organization of Economic Cooperation and Development (OECD) countries, though many initiatives involve partnerships with firms and other institutions in developing countries.

The idea that developing countries can and should play a leading role in the development of medicines to meet the needs of their populations is not new.[5] This goal is enshrined in international consensus documents, such as the Global Strategy and Plan of Action on Global Health, Innovation, and Intellectual Property, adopted by the World Health Organization's (WHO's) World Health Assembly in 2008, which states that "strengthening of the innovative capacity of developing countries is essential to respond to

[1]Waning, B., Diedrichson, E., & Moon, S. (2010). A lifeline to treatment: The role of Indian generic manufacturers in supplying antiretroviral medicines to developing countries. *J Int AIDS Soc 14*(13): 35.

[2]Serum Institute of India's website: www.seruminstitute.com.

[3]See in particular the work of the McLaughlin-Rotman Centre for Global Health at the University of Toronto, including Frew, S. E., Kettler, H. E., & Singer, P. A. (2008). The Indian and Chinese health biotechnology industries: Potential champions of global health? *Health Aff* 27(4): 1029–41. Frew, S. E., Liu, V. Y., & Singer, P. A. (2009). A business plan to help the "global South" in its fight against neglected diseases. *Health Aff* 28(6): 1760–73. Frew, S. E., Rezaie, R., Sammut, S. M., Ray, M., Daar, A. S., & Singer, P. A. (2007). India's health biotech sector at a crossroads. *Nat Biotechnol 25*(4): 403–17. Rezaie, R., & Singer, P. A. (2010). Global health or global wealth? *Nat Biotechnol 28*: 907–09.

[4]See Frew, Kettler, & Singer (2008). See also Drugs for Neglected Diseases Initiative's (DNDi's) 2012 policy brief on the need for an R&D convention, titled "Transforming individual successes into sustainable change to ensure health innovation for neglected patients: Why an essential health R&D convention is needed."

[5]The contributions that are the focus of this report go beyond endemic country involvement in priority setting, definition of product needs, and clinical trials. These roles, though critical, do not require specialized capacity in modern health technology discovery and product development.

the needs of public health."[6] The recent report of the WHO's Consultative Expert Working Group on R&D Financing and Coordination emphasizes the obligation of both developing and high-income countries to contribute to the financing of global health R&D.[7]

Although this notion is intuitively appealing and may seem self-evident, it is worth reviewing some of the arguments that have been made for relying more on innovators in developing countries to meet neglected disease R&D needs, as well as for building health R&D capacity in these countries. Some of these arguments may be more compelling to developing country governments, whereas others may be more relevant to donors.

One argument is self-reliance: health is—or should be—a national priority, and it is too risky to rely for urgently needed new technologies on others who may not share your needs and priorities. Every country, this argument goes, should take responsibility to the greatest extent possible for meeting its own health needs. This position accords well with the principle of country-led development both in health and in other areas. Moreover, and crucially, the concept of self-reliance is closely linked to the principle that countries should set their own priorities for health development and thus for health R&D.

It may or may not follow from this normative argument that developing country governments, scientists, and even companies will naturally have a stronger interest in addressing the health needs of their own populations, including those of the poor, than will innovators (in particular, multinational companies) based in the West. This may, in turn, mean that local researchers and firms will be more willing to work on these problems, even when they offer less commercial reward than projects focused on more lucrative markets. The extent to which this is the case needs to be determined.

Even if emerging-market firms are motivated only by commercial considerations, their business models, which are focused less on blockbusters and more on high-volume, low-margin products, may make certain global health products more attractive to them than to multinationals.

Another important argument is that developing-country innovators may be able to do needed health R&D more cheaply than it could be done in the United States or Europe, just as firms in India and elsewhere clearly enjoy a cost advantage in producing certain drugs and vaccines. To the extent that this is true, it would make sense for international donors interested in global health R&D to direct resources toward developing-country innovators and, perhaps, to invest in expanding the capacity of these innovators.

Researchers and product developers in developing countries could enjoy other advantages, including greater access to patients and patient samples, greater knowledge of the relevant diseases, and greater familiarity with specific product needs, including product characteristics appropriate for low-resource settings.

Finally, R&D and access may be linked in important ways, so that a product developed in India or China may be more likely to reach those who need it not only in those countries but also perhaps in other low- and middle-income countries.

National governments may also see a strong case for building biotechnology industries as a matter of industrial policy. However, this is not, in itself, a public health consideration, even though investment in strengthening domestic R&D capacity can bring

[6]WHO. (2008). *Global Strategy and Plan of Action on Public Health, Innovation and Intellectual Property. Sixty First World Health Assembly, Agenda Item 11.6*: 8.

[7]WHO. (2012). *Research and Development to Meet Health Needs in Developing Countries: Strengthening Global Financing and Coordination.* Report of the Consultative Expert Working Group on Research and Development: Financing and Coordination (Geneva: World Health Organization).

public health benefits if the increased capacity is directed toward public health needs.

Each of these arguments undoubtedly holds in some circumstances. But each raises important questions.

- Most obviously, for which R&D projects (which products and which types of R&D) do developing-country researchers and firms have the necessary capacity? Health research and drug and vaccine R&D is complicated, expensive, and highly regulated. Even in the United States and Europe, fewer and fewer firms have the skills and resources to bring a new drug or vaccine from concept to market. In countries such as India, firms are likely to be able to contribute in some areas but not in others.
- From the perspective of international donors, when is working with product developers in India or other innovative developing countries more efficient or less costly than working with partners in the United States or Europe? Will investing in the R&D capacity of these firms now pay off later in the form of more efficient neglected disease product R&D? From the perspective of the Indian government, when does it make sense to support domestic research on a needed health technology rather than contributing to international efforts to develop the product?

The idea that every country should strive for self-sufficiency in all-important industrial areas has been largely abandoned as a formula for economic development, though it is still invoked in "strategically important" sectors. To what extent should it hold for health R&D?[8] The WHO has recently commissioned papers looking at local production of drugs, vaccines, and diagnostics; to differing extents, these papers also address local product development.[9]

- Are firms based in India or China more interested in products for their home markets than are multinational companies? Does this interest extend to products for the poor or for other developing countries? Will interest fade as these firms gain access to international markets? What happens when local firms are acquired by multinationals?
- Is it true that developing country firms have lower R&D costs, even when the sophistication of the required R&D and the probability of success are factored in? What will happen to R&D cost advantages as skilled researchers and managers increasingly move internationally and as salary gaps shrink?
- Will the business models of developing-country firms change as they invest more in R&D and pursue opportunities in high-income countries? Will they come more and more to resemble U.S. or European multinationals in their R&D priorities and commercial calculations?

This report takes up these questions. It cannot, of course, provide definitive answers to all of them, and it should be considered a landscaping study—that is, an overview of opportunities and constraints for global health R&D in India. We attempt to frame important questions, critically examine some widely held beliefs, and highlight areas for further study. We also offer some preliminary recommendations for global health R&D funders and other international stakeholders, as well as for agencies of the Indian government concerned with health R&D. However, in many areas, robust recommendations will require more in-depth analysis.

In this report, we focus largely on the development of new technologies for diseases primarily affecting people in low- and middle-income countries—type II and III diseases, in the terminology of the WHO's Commission on Macroeconomics

[8]The WHO reports can be found at www.who.int/phi/publications/local_production/en/index.html.

[9]Moon, S. (2011). *Pharmaceutical Production and Related Technology Transfer* (Geneva: World Health Organization). Gong, W., Freide, M., and Sparrow, E. (2011). *Increasing Access to Vaccines Through Technology Transfer and Local Production* (Geneva: World Health Organization). Peeling, R., & McMemey, R. (2011). *Increasing Access to Diagnostics Through Technology Transfer and Local Production* (Geneva: World Health Organization).

and Health—including malaria, tuberculosis, and neglected tropical diseases.[10] This is because, as is broadly recognized, the current health R&D system, driven by public-sector expenditure in wealthy countries and industrial investment motivated by large patent-protected markets, is particularly ill-suited to developing needed products for these diseases. In this sense, the report asks how India can help fill this particularly glaring gap in the system. Countries such as India also suffer from a high burden of noncommunicable disease, however, and Indian researchers and companies may be in a very good position to develop new and better-adapted tools to address these diseases as well. This is an important area for future work.

Finally, we recognize that the global R&D system as currently constituted does an imperfect job of meeting the most urgent health needs of populations in high-income countries too and is plagued by a range of inefficiencies and perverse incentives. Even on its own terms, the drug industry in particular is increasingly concerned that its R&D model is not yielding the hoped-for flow of new products. Against this background, the development of innovation systems in India and similarly situated countries could offer opportunities not only to fill specific R&D gaps related to diseases of the poor, but also to pioneer new models that might ultimately work better to meet a broad range of health needs in rich and poor countries alike. This prospect has not been a focus of our research for this paper, but in considering both what India can contribute and how Indian innovation policy could be improved, it is worth keeping in mind that the innovation systems of the United States and Europe are by no means an ideal model and that India has a chance to learn from the mistakes, as well as the successes, of other countries.

This report focuses on India, but the basic rationale for the work applies equally well to other developing countries with growing health R&D capacity—in particular, China. We briefly consider the implications of our findings for other countries in the last section.

Although we look only at India, our scope is broad in other ways. We consider the three major classes of health technologies: drugs, vaccines, and diagnostics.[11] We also consider a broad range of R&D, from discovery stages (but not basic research) through clinical trials and manufacturing process development, as well as both incremental product development such as new formulations and combinations and development of entirely new products such as new chemical entities. We include within our scope the development of follow-on vaccines—vaccines based to a large extent on existing products but requiring independent testing and regulatory approval—but not generic or biosimilar drugs.

We focus primarily, but not exclusively, on product development in industry and thus primarily on the private sector (and on state-owned firms where they are active in new product development). However, we also consider ties between public-sector and university research and industry.

The study has three overall objectives:

- To understand where India, and especially Indian industry, can contribute to the development of needed new drugs, vaccines, and diagnostics for the poor, in India as well as in other developing countries, and to anticipate how this capacity is likely to evolve.
- To understand how Indian industry can best be engaged by the Indian government or international donors to achieve health R&D goals.
- To identify the most important obstacles to neglected disease health R&D in India and recommend ways that the Indian government or international partners might ease these obstacles.

[10]We use the terms *neglected disease* and *global health R&D* rather loosely. Our focus throughout is on infectious diseases and on products needed by poor populations in low- and middle-income countries. We also consider vaccines against rotavirus, childhood pneumonia, and human papillomavirus (HPV): although these diseases are global and the vaccines are used in high-income countries, their health impact is greatest in poor countries.

[11]We do not look at in vivo diagnostics or devices.

Our findings and recommendations are derived from review of published literature and from interviews with a broad range of Indian and international experts, researchers, and industry executives. For a list of interviews, see Annex II.

Section 2 provides an overview of some general elements of the health innovation system in India and some of the broad challenges to health R&D, such as gaps in financing and regulatory policy. Sections 3–5 then look separately at the three main product areas—vaccines, drugs, and diagnostics—which differ in important ways. In Section 6, we summarize our most important findings and put forward some preliminary recommendations.

CHAPTER 2
THE SUPPORTING ENVIRONMENT FOR BIOMEDICAL INNOVATION

2

India is in the midst of a sustained transition. Recent governments have eased some of the restrictions on business and foreign investment that were put in place in the decades after independence, and in turn, a strong private sector has emerged.

The economy has expanded consistently since the late 1990s,[12] and some sectors of Indian industry have thrived in international markets.

These changes in economic policy and orientation have been accompanied by a growing emphasis on innovation, in both the public and the private sector. All innovation-based industries, including biotechnology and pharmaceuticals, require a range of enabling inputs that can support the creation, adaptation, and diffusion of new technologies.[13] Some of these elements of the innovation system include adequate numbers of well-trained scientists and engineers, availability of financing for R&D, a robust but not excessively burdensome regulatory system, and strong linkages between publicly funded research and private industry. If these pieces are not in place, then India will struggle to expand its contribution to R&D for neglected disease. Although there are differing views on how national innovation systems come together and which components are most important, there is general agreement that innovation is the result of complex interactions between public and private institutions.[14] We will not attempt a comprehensive analysis of India's innovation system, but we do highlight in this section a few general areas that emerged as important issues for biomedical R&D in our interviews and analysis.[15] Some issues specific to particular product areas are addressed in the succeeding sections.

Human Resources

India produces about 2.5 million science and engineering graduates each year,[16] a million more than China. India's large pool of skilled workers—and low salaries compared to the United States and Europe—is often cited as an important strength.[17] Even so, it is far from clear that there are enough people with the right skills to effectively devise, carry out, and manage biomedical R&D initiatives in India. According to a World Bank report, "The widespread perception that India has unlimited employable human resources has changed. India has a growing shortage of skilled

[12]"Indian politics: Unfinished journey." *The Economist*, March 24, 2012.

[13]Milbergs, E. (2007). *Innovation Vital Signs: Framework Report: An Update.* Center for Accelerating Innovation. Vers. 2.8, available at: www.innovationecosystems.com/images/Innovation_Vital_Signs_Framework_Report_v.2.8.pdf.

[14]Lundvall, B.-A. ed. (1992). *National Innovation Systems: Towards a Theory of Innovation and Interactive Learning* (London: Pinter). Edquist, C. ed. (1997). *Systems of Innovation: Technologies, Institutions and Organizations* (London: Pinter). Herstatt, C., Tiwari, R., Ernst, D., & Buse, S. (2008). *India's National Innovation System: Key Elements and Corporate Perspectives* (East-West Center Working Paper 96, Honolulu).

[15]For examples of analyses of India's innovation system, see Dutz, M. ed. (2007). *Unleashing India's Innovation: Toward Sustainable and Inclusive Growth* (Washington, DC: World Bank). Herstatt et al. (2008). National Knowledge Commission. (2007). Innovation in India. (New Delhi: GOI)

[16]Bound, K. (2007). *India: The Uneven Inventor.* (London: Demos—The Atlas of Ideas).

[17]Herstatt, C., Tiwari, R., Ernst, D., & Buse, S. (2008). *India's National Innovation System: Key Elements and Corporate Perspectives* (East-West Center Working Paper 96, Honolulu). World Economic Forum. (2011). *Global Competitiveness Report 2011–2012* (Geneva: World Economic Forum).

workers—caused largely by workforce development and education systems that do not respond adequately to the economy's needs."[18] Moreover, there are gaps and imbalances in workers' competencies. For example, the Indian education system is traditionally much stronger in chemistry, which encompasses only a selection of the skills needed for the full spectrum of biomedical R&D, than biology. Moreover, some allege that a culture of taking risks and accepting failure, which is crucial for supporting new ideas, is not well developed in India, including among managers.[19]

Many key research staff at Indian drug and vaccine firms have at least some training or experience abroad, which is a critical way of building skills and know-how. As the biotechnology and pharmaceutical industries grow and as the economy develops more broadly, it is reasonable to assume that more Indian scientists and industry professionals will consider returning to India, as has apparently happened in the information technology industry. However, this flow of highly skilled people will also accelerate the convergence of salaries.

Industry executives interviewed for this report expressed mixed views on the availability of skilled personnel for their R&D programs. Although many executives said they were able to find the people they needed, some complained about a lack of practical training at Indian universities and about the lack of higher-level skills required for innovation. Some international experts mentioned lack of experienced research managers as a specific deficiency. A number of programs supported both by international partners and the government of India (GOI) offer young scientists the opportunity to spend time with domestic industry or to collaborate with institutes abroad, but the scale of these initiatives is small.[20] The government is making longer-term investments by creating new national pharmaceutical institutes and strengthening existing ones, as well as by developing biotechnology programs in universities.[21] However, these promising initiatives will take several years to bear fruit.

In addition to concerns about quality, there is widespread agreement that the cost of good people is rising, as top students have many opportunities domestically and abroad. Although many firms are willing to pay steadily increasing salaries to retain good staff, the cost of personnel may limit the amount of time that staff can spend on projects with small returns, such as those pertaining to neglected diseases, if there are competing priorities that promise high returns.

Financing of Pharmaceutical and Biotechnology R&D

Public Sector

The GOI is committed to supporting the expansion of R&D in the pharmaceutical and biotechnology industries and has taken a direct role in funding R&D in both the public and private sectors. In 2005–2006, the central government was responsible for 57.5 percent of all national R&D expenditure, and total government expenditure, which includes state spending, accounted for 74.1 percent of R&D spending.[22] In contrast, in the United States, federal funding constitutes a little more than one-quarter of all R&D funding, reflecting much greater private-sector R&D expenditure.[23] Indian central government R&D

[18]Froumin, I., Divakaran, S., Tan, H., & Savchenko, Y. (2007). Strengthening skills and education for innovation. In Dutz, M. ed. (2007). *Unleashing India's Innovation: Toward Sustainable and Inclusive Growth* (Washington, DC: World Bank)

[19]Krishnan, R. (2011). Barriers to innovation in India. Presentation at TB Diagnostics in India: From Importation and Imitation to Innovation (Bangalore, August 25–26, 2011).

[20]Singh, S. (2009). Building public-private research partnerships in troubled times. *Cell 136:* 987–89.

[21]Government of India (2011). *National Planning Commission Report on Drugs and Pharmaceuticals* (New Delhi). Interviews

[22]Government of India. (2008.) *R&D Statistics 2007–2008* (New Delhi: Department of Science and Technology).

[23]Ibid.

Table 2.1: Budgets of Indian Government Ministries and Departments Funding Biomedical Research

Government Body	2010–2011 Actual Expenditure	2012–2013 Total Budget
Ministry of Science and Technology	$1,013,634,600	$1,302,550,000
Department of Biotechnology	$244,279,900	$323,730,000
Department of Scientific and Industrial Research*	$347,984,680	$438,834,000
Department of Science and Technology	$421,367,840	$539,986,000
Ministry of Family Health and Welfare	$4,518,363,920	$6,643,986,000
Department of Health Research**	$112,296,160	$143,880,000
Ministry of Chemicals and Fertilizers	$537,354,740	$1,150,231,220
Department of Pharmaceuticals	$15,188,060	$40,984,000

*Houses the Council of Scientific and Industrial Research (CSIR) but excludes about $300 million of CSIR spending.

**Houses ICMR but excludes about $52 million of ICMR spending.

Source: Union Budget 2012–2013, Plan Outlay, Government of India.

funding reached 28,776.65 crore[24] rupees that year (about $6.33 billion), but the majority of this flowed to the defense, space, and energy sectors.[25] The total amount of R&D funding remains small in comparison to that of the U.S. federal government, which spent about $100 billion on R&D in 2010. However, the GOI's spending does demonstrate a strong commitment to innovation.[26]

For health R&D, much of the GOI's funding flows through the Ministry of Science and Technology and the Ministry of Health and Family Welfare. The Ministry of Science and Technology oversees the Department of Biotechnology (DBT), the Department of Scientific and Industrial Research (DSIR), and the Department of Science and Technology (DST), all of which play an important role in funding research. DBT is the largest central government funding agency for the life sciences in India.[27] The Ministry of Health and Family Welfare houses the Indian Council of Medical Research (ICMR) and the Drug Controller General of India (DCGI). Table 2.1 details the expenditure and current budget for the main departments and ministries involved in health research.

ICMR funds a number of public research institutes and monitors and supports clinical trials. DCGI is responsible for regulating new health products. Dozens of research institutes fall under the purview of DBT, DSIR, and ICMR, and much of the public-funded research that takes place in India occurs within these institutes rather than in universities.

[24]One crore is equal to ten million

[25]Ibid. Srinivas, S., & Tanaku, K. (2011). *Research to marketplace linkages: A call to action.* Wahdwhani Centre for Entrepreneurship, Indian School of Business.

[26]Batelle, *R&D Funding Forecast 2011,* 2010.

[27]Singh, S. (2009). Building public-private research partnerships in troubled times. *Cell 136:* 987–89.

Table 2.2: Indian Government Expenditure on Neglected Disease R&D

Government Agency	2010 Neglected Diseases Funding
ICMR	$17,178,281
DBT	$9,742,057
CSIR	$3,957,939
GOI Support to WHO's Special Programme for Research and Training in Tropical Diseases	$23,769

Source: G-FINDER 2012.

In 2007, the GOI revamped its National Biotechnology Development Strategy and allocated more funding to programs supporting public-private partnerships.[28] Annex II profiles the most prominent programs to support health R&D within firms such as the Biotechnology Industry Partnership Programme, the New Millennium Indian Technology Leadership Initiative, and the Small Business Innovation Research Initiative. These programs tend to have the dual objectives of accelerating the development of technologies needed in India and supporting industrial development. They include a mix of soft loans and grants, with grants most commonly flowing to public partners.

Many firms interviewed for this report have benefited from these programs and commend the government's efforts to engage industry. However, some find that the process for securing public funding is too bureaucratic, that personal connections play too large a role in project selection, and that funding comes with too many restrictions. In general, new firms do not have access to public funding, as these programs usually require DSIR certification of R&D activities, which involves demonstrating a three-year history of R&D operations. However, if successful, a new "ignition grants" program that DBT is developing to support start-ups could soon help meet this need.[29] Interviewees also contend that project review committees are staffed with public researchers who are unfamiliar with commercial product development. In contrast, specialists within the public funding programs argue that there are too few industry projects that warrant support.

The emphasis on creating technologies that meet India's needs has led the government to fund some neglected disease projects, especially in malaria and tuberculosis (TB), but it is unclear how health priorities are weighed against economic or industrial policy objectives when allocating resources. According to the neglected disease R&D tracking study Global Funding of Innovation for Neglected Diseases (G-FINDER), the GOI contributed about $31 million to research on the set of infectious diseases included in the survey in 2010.[30] The neglected disease R&D expenditure of individual government agencies is noted in Table 2.2. Since neglected diseases have small product markets and are less likely to attract private-sector financing, these programs are particularly important for product developers interested in diseases of the poor.

[28]Frew, S. E., Kettler, H. E., & Singer, P. A. (2008). The Indian and Chinese health biotechnology industries: Potential champions of global health? Health Aff 27(4): 1029–41. For a recent analysis of DBT's programs, see Vijayaraghavan, K., & Dutz, M. A. (2012). *Biotechnology Innovation for Inclusive Growth: A Study of Indian Polices to Foster Accelerated Technology Adaptation for Affordable Development*, (World Bank Policy Research Working Paper 6022: Washington, DC).

[29]Vijay, N. (2011). DBT to come out with Ignition Grant for start up projects by year end, Rs.500 cr to be disbursed initially. *Pharmabiz*. Accessed June 11, 2012; available at http://pharmabiz.com/ArticleDetails.aspx?aid=66078&sid=1. Interviews.

[30]G-FINDER, accessed April 2012, available at http://g-finder.policycures.org/gfinder_report/.

Box 2.1: R&D for Affordable Healthcare in India

In 2010, the Wellcome Trust and the Department of Biotechnology (DBT) in India launched a joint program to identify and support innovative R&D projects that may result in low-cost products that meet the country's public health needs. The program funds both public-sector institutes and industry and targets communicable and noncommunicable disease.

The program has supported about 14 projects, including the development of a "smart cane" for individuals with visual impairment, early-stage R&D for a new TB treatment, and the completion of clinical trials to evaluate the effectiveness of a "poly pill" for preventing cardiovascular disease. The program prioritizes translational research and seeks out projects that have the potential to be commercialized.

The government of India is establishing a special-purpose vehicle that grants shared oversight of the program to the Wellcome Trust and DBT, letting the program benefit from the knowledge and network of DBT while retaining the flexibility of an international funding initiative. Each partner has pledged £22.5 million, allowing the program to support up to £45 million worth of R&D in its first phase.

Sources: Interviews ."R&D for Affordable Healthcare in India," available at: http://www.wellcome.ac.uk/Funding/Technology-transfer/Funded-projects/India/index.htm Accessed 6 Jun 2012

Private Sector

Private equity (PE) and venture capital (VC) investment is growing in India. Total PE deals in India reached about $7.9 billion in 2010; for comparison, deals in the United States totaled $132 billion in the same year. Most PE investors in India target the real estate, information technology, and infrastructure sectors; investments in pharmaceutical and biotechnology R&D have not kept pace.[31] More recently, however, investors are beginning to pursue investments in the life sciences, though the volume of deals is still low.[32] The World Bank Group was catalytic in seeding the VC industry in India; in fact, the International Finance Corporation (IFC) remains one of the most significant PE investors in the country.[33] In 2010, the IFC made $223.4 million worth of PE investments in India across 14 deals, which is about $62 million more than the next top PE investor.[34]

When investors do fund life science firms, they usually support mature projects rather than early high-risk work.[35] Although social impact investing, or investing in businesses or organizations that pursue both financial and social returns, is also gaining currency in India, so far, social businesses in India tend to follow a health service–based business model or market technologies that require considerably less R&D than drugs or vaccines.[36]

Recognizing that overall investment in the life sciences has been low, the government of Andhra Pradesh partnered with Dynam Ventureast to launch a $37 million venture fund dedicated to biotechnology investments.[37] After the fund's establishment, the World Bank Group's IFC contributed $4 million in equity to it.[38] The fund's activities are not limited to health—in 2004, it provided about $17.7 million to biotech firms.[39]

[31]Grant Thornton (2011). The Fourth Wheel Private Equity in the Indian Corporate Landscape. Venture Intelligence (2009). Private Equity Pulse on Healthcare and the Life Sciences.

[32]Naru, S. Presentation. The biotech investment opportunity in India. Presentation at ADIPC Venture Capital Limited

[33]Bowonder, B., & Mani, S. (2002). Venture capital and innovation: The Indian experience. UNU/INTECH research report presented at the International Conference (Brussels, November 7–8, 2002). Grant Thornton (2011).

[34]Grant Thonton (2011).

[35]Naru. Interviews.

[36]Allen, S., Bhatt, A., Ganesh, U., & Kulkarni, N. K. (2012). On the path to sustainability and scale: A study of India's social enterprise landscape. *Intellecap* (April).

[37]Naru.

[38]Fan, P. (2008). The rise of the Indian biotech industry and innovative domestic companies. *Int J Technol Globalisation 4(2)*: 148–69.

[39]Kumar, N. K., et al. (2004). Indian biotechnology: Rapidly evolving and industry led. Nat Biotechnol 22: DC31–36.

Recently, the National Innovation Council announced its intent to create a $1 billion inclusive innovation fund to invest in businesses that yield both economic and social returns.[40] This fund, which has yet to launch, will target many sectors, including health.

Across sectors, investors tend mostly to support late-stage or low-risk deals in India; early-stage investments are growing slowly.[41] Some suggest that this slow growth reflects an aversion to risk, but it may owe more to an abundance of low-risk yet high-return opportunities. (In this sense, a shortage of high-risk capital may be a by-product of India's rapid growth.) An analysis of drug firms found that returns to equity are greater for companies with a high level of exports.[42] These firms are likely large generics firms rather than companies focusing on early-stage R&D. Early-stage deals may increase as more investors enter the Indian market and crowd out late-stage opportunities.

Our interviews also suggest that privately held biotech firms are reluctant to give up equity in return for capital and prefer slower growth to losing strategic control of the company. Many firms finance R&D through their own revenues, which limits the scale of R&D projects but allows senior management to pursue their desired R&D strategies.

The lack of financing for high-risk early-stage work may be one of the biggest barriers to innovation and may most affect entrepreneurs who want to start new R&D-driven businesses. Although PE and VC investors do not normally invest in neglected disease projects, the lack of capital for early-stage enterprises may limit the emergence of technologies that could ultimately be applied to diseases of the poor. For instance, a diagnostic company may be interested in developing a new platform that runs point-of-care tests for type I diseases but that could also perform assays for neglected diseases. If such a company cannot secure early-stage investment, then a potentially important public health opportunity would be missed.

Investments in early-stage high-risk biomedical R&D can lead to unforeseen technologies for neglected diseases. Donor programs that target funding to industry for projects important to public health, such as the Bill and Melinda Gates Foundation's Grand Challenges program or the Wellcome Trust's R&D for Affordable Healthcare Initiative (described in Box 2.1), are critical for narrowing this financing gap, but the larger unmet need for financing persists.

Intellectual Property

India eliminated product patents on medicines in the 1970s. But with the implementation of the agreement on Trade Related Aspects of Intellectual Property Rights (TRIPS) in 2005, Indian firms are now subject to a patent regime similar to those prevailing in the United States and Europe. The change in patent regime has had profound effects on the business models of drug firms in particular and potentially significant implications for affordable access to some important medicines. In general, however, it has less of an impact on R&D, particularly for neglected disease products, for which commercial stakes are generally low. Yet patents can be an obstacle to the development of adapted versions of existing drugs, such as new formulations or combinations, and to the development of follow-on versions of vaccines, especially those with global markets. Even when patents do not block the development of a new product, the increasing complexity of intellectual property (IP) landscapes can be challenging for Indian firms to navigate.

In our interviews, most firms claimed that IP is not a major barrier to R&D, though vaccine firms reported that in some cases the need to work around patents had imposed additional costs. Firms and research institutes have also begun to more regularly patent their own work. As shown in Figure 2.1, patenting in all fields is on the rise in India. Drug patents

[40]National Innovation Council. (2012). India to launch $1-bn Innovation Fund by June–July, available at www.innovationcouncil.gov.in/index.php?option=com_content&view=article&id=150:india-to-launch-1-bn-innovation-fund-by-june-july-news&catid=14:news&Itemid=13.

[41]Indian Private Equity and Venture Capital Association. (2007). Venture capital and private equity in India. Presentation.

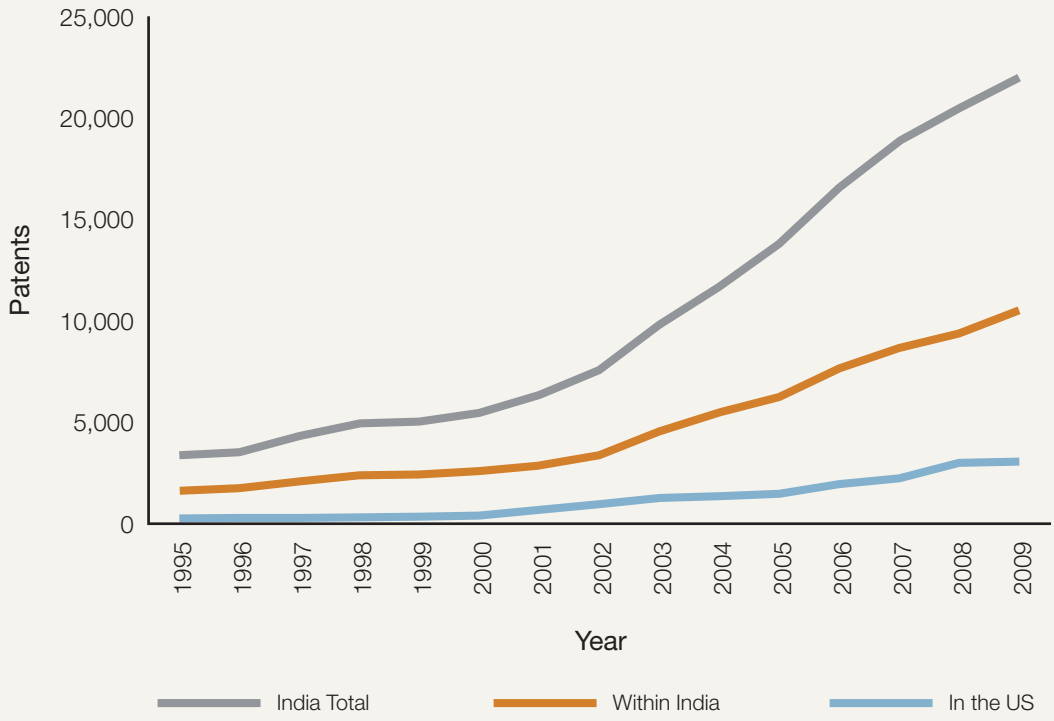
[42]Chaudhuri, S. (2010). The Indian pharmaceutical industry after TRIPS. In Chaudhuri, S., Park, C., and Gopakumar, K. M. eds. *Five Years into the Product Patent Regime: India's Response* (New York: United Nations Development Program).

have more than doubled since 2001, and patents in biotechnology have almost reached the same levels, though the growth rate for biotechnology patenting has increased considerably.[43]

Although India has implemented product patents, one notable difference between Indian patent law and that of the United States is that India has more stringent standards on secondary patents. The 2005 Patent Amendments Act does not grant new patents for new uses of a known substance or for modifications to a drug unless the changes make the drug significantly more efficacious. These flexibilities allow Indian companies to market some generic drugs in India more quickly, as shown by the much-contested case of Novartis's Gleevec and Cipla's challenge of patents held by Bayer and Roche. However, our interviews suggest that they do not offer clear-cut advantages for new product development in India.[44]

In discussing the impact of the 2005 changes in Indian patent law, it is important to distinguish the narrow question of whether firms, which on the whole have adapted to the new regime, perceive patents as an obstacle to their current business models and the broader issue of whether a different patent regime could better serve social goals in innovation and access to medicines. This larger question, which requires a close look at the global IP system and rewards to innovation, is outside the scope of this study.

Figure 2.1 Patents Filed from India



Source: WIPO Statistics, 2100

[43]EvalueServe. (2009). *Study on R&D Ecosystem in India.* Report commissioned by the British High Commission and Canadian High Commission (New Delhi).

[44]Nolen, S. (2012). Drug companies watching India's patent case. The Globe and Mail, available at: www.theglobeandmail.com/news/world/shareTweet/article2380845/. Chaudhuri, S. (2010). The Indian pharmaceutical industry after TRIPS. In Chaudhuri, S., Park, C., and Gopakumar, K. M. eds. *Five Years into the Product Patent Regime: India's Response* (New York: United Nations Development Program).

Public-Private Linkages

Public and Academic Research

India has a large public research network with increasing scientific outputs. Publications are on the rise—India produced about 3 percent of the world's science publications between 2004 and 2008. In comparison, however, China has overtaken most European countries and Japan with 10 percent of the world's scientific publications.[45] Despite the increase in publishing, the value of public research for product development is uncertain, as linkages with industry that result in technology transfer and product development remain weak.[46] It is important to find ways to advance this work into industry, because much of the neglected disease research that takes place occurs in public and academic institutes.[47]

A survey of 83 executives found that the lack of collaboration between the public and private spheres is viewed as one of the main obstacles to innovation in India.[48] Although the government has many programs to finance public-private collaborations, firms allege that the technology created in the public sector is not sufficiently advanced for commercialization or is unlikely to result in viable products. Unlike in the United States, few biotech companies in India are spun off from public or academic scientific institutions.[49] Some interviewees implied that in the public sector, publications are more valued than research that leads to product development, though this observation is not unique to India. Legislation similar to the U.S. Patent and Trademark Law Amendments Act (the Bayh-Dole Act), which encourages the commercialization of intellectual property developed in academia with public funding, has long been debated in India.[50] The legislation intends to improve and standardize technology transfer and commercialization, in addition to increasing awareness about the potential of IP in the public sector. However, experts have expressed reservations about the ability of the act to achieve these objectives.[51] India has yet to adopt policies to meet these goals.

Public Procurement Priorities

For many firms, public procurement of health commodities is an important component of the domestic market and can serve as an incentive for new product development. Interviewed firms stressed that the GOI's public health programs do not send clear signals regarding what new technologies they would like to adopt. India lacks a central agency—or network of agencies—that assesses whether new health technologies are cost effective for the public health system. Firms also explained that public tenders and volume requirements are difficult to predict. For drugs, there is no central procurement agency for the government; instead, individual states drive procurement decisions.[52] This lack of knowledge regarding adoption of new products and uncertainty of market size deters firms from developing products targeted at domestic public health programs.

[45]Royal Society. (2011). *Knowledge, Networks and Nations Global Scientific Collaboration in the 21st Century* (Royal Society Policy Document, London).

[46]Ray, A. S. (2004). The changing structure of R&D incentives in India: The pharmaceutical sector. *Science, Technology, and Society 9:* 925. Visalakshi, S. Capabilities in Commercialisation of Biotechnology in India: An Analysis. (National Institute of Technology and Development Studies report: New Delhi). Dutz, M. ed. (2007). Unleashing India's Innovation: Toward Sustainable and Inclusive Growth (Washington, DC: World Bank).

[47]Ganguly, N. K., Mukhopadhyay, B., Gupta, S. S., and Bharati, K. (2010). *Mapping of Health Products R&D Landscape for Infectious Tropical Diseases in India.* (National Institute of Immunology, New Delhi, India).

[48]Dutz, M. ed. (2007). *Unleashing India's Innovation: Toward Sustainable and Inclusive Growth* (Washington, DC: World Bank).

[49]Ibid. Interviews.

[50]Basheer, S. (2010). Outsourcing "Bayh-Dole" to India: Lost in transplantation? *Columbia Journal of Asian Law 23*(2): 269–313.

[51]Sampat, B. N. (2009). The Bayh-Dole Model in Developing Countries: Reflections on the Indian Bill of Publicly Funded Intellectual Property (UNCTAD-ICTSD Policy Brief 5, Geneva).

[52]Jeffery, R., & Basu, S. , Bhattarai, S., Brhlikova, P., Das Gupta, A., Ecks, S., Harper, I., Jefferey, P., Pollock, A., Singh N. & Subedi, M.S. (2007). Pharmaceutical Distribution Systems in India (Centre for International Public Health Policy Working Paper 1a: Edinburgh, Scotland).

Regulatory Environment

India presents a complicated regulatory landscape for health technologies, especially those involving biotechnology and genetically manipulated organisms. At least three ministries, as well as a number of smaller departments or agencies, have some role in regulating biomedical R&D. The DCGI, under the Central Drugs Standard Control Organization, coordinates regulatory review with support from many other government bodies. Annex II provides an overview of the main bodies involved in regulation.

Firms complained that the regulatory system is not designed to assess the risks and benefits of new products, most notably evidenced by a reluctance to approve first-in-human trials, and that regulators follow an inflexible framework that is poorly suited to novel technologies. In addition, firms noted that unlike the U.S. Food and Drug Administration (FDA), the DCGI does not provide opportunities for firms to seek guidance as a product is being developed regarding what the firms would have to demonstrate to win approval. On the positive side, however, some evidence indicates that review times are gradually decreasing, though they remain long.[53] Approval for a phase I trial for a new chemical entity (NCE) takes between five and eight months in India, compared with only 30 days in the United States.[54] As Indian firms move into new technologies, regulatory frameworks will have to evolve. Currently, India, like many other countries, lacks a clear regulatory pathway for biogenerics (or "biosimilars"), which is a growing area of interest for Indian firms.[55]

In addition to long timelines for regulatory review and fragmented responsibility, the quality of regulation in India has been called into question.56 Some firms complained that regulators do not have a sufficient understanding of the relevant science. The division of responsibilities among central, state, and local authorities and capacity constraints at the DCGI have led to quality gaps and the presence of inferior drugs and diagnostics, especially in the private health sector. States are responsible for granting and renewing manufacturing licenses and for inspecting manufacturing facilities.[57] There is no mechanism in place to standardize the ethical review of trials, and recent reports suggest that clinical trials are responsible for undue mortality.[58] From a public health perspective, inferior technologies perpetuate the incidence of disease and breed resistance to effective treatments. Without efficient mechanisms to remove bad products from the market, high-quality technologies must compete with inferior products in private markets. This issue is discussed in Section 5 in regard to TB diagnostics.

Although DBT is advocating for streamlined and centralized review of new biotechnology products, there is limited momentum toward improving the review channels for drugs and diagnostics.[59] The DST has pushed for reform that strengthens the review and approval of devices, including diagnostics, but proposals have not made it into law. Since new and more effective neglected diseases technologies are urgently needed and could result in immediate public health impact, it is essential that the government swiftly implement initiatives to streamline and strengthen regulation, in addition to assessing and responding to any gaps that persist.

[53]Jayasheel, B. G. (2010). Carrying out clinical trials in India. *Raj Pharma* [regulatory feature]. Available at: www.acunovalife.com/pdf/whitepapers/RAJ_Pharma%20June%202010_Jayasheel%20final.pdf

[54]Ibid.

[55]Gulse, J. W., & Carson, B. M. (2009). Biogeneric regulatory policies in China and India: A comparative study. *Regulatory Affairs 44:* 55–67.

[56]Pai, M. (2011). Tuberculosis control in India: Time to get dangerously ambitious? National Medical Journal of India [editorial] 24(2): 243–44. Government of India. (2003). *A Comprehensive Examination of Drug Regulatory Issues, Including the Problem of Spurious Drugs* (Delhi: Ministry of Health and Family Welfare).

[57]National Planning Commission. (2011). *Working Group Report on Drugs and Food Regulation for the 12th Five-Year Plan*. Available at: http://planningcommission.nic.in/aboutus/committee/wrkgrp12/health/WG_4drugs.pdf.

[58] Overdorf, Jason (2012, July 9). India: 10 die per week in drug trials. *Global Post*. Accessed 20 July 2012; available at http://www.globalpost.com/dispatches/globalpost-blogs/india/drug-trials-world-health-organization.

[59]Reddy, V. K. I. (2009). Biotech regulation in India: Problems and promises. *Biotechnol J 4:* 306–09.

Infrastructure

Interviewees explained that the basic infrastructure for laboratories—from consistent power to uninterrupted water—is costly and difficult to obtain in India. In addition, a survey conducted for the World Economic Forum's Global Competitiveness Report found inadequate supply of infrastructure to be the single most problematic factor for doing business in India.[60] Another survey of more than 4,000 firms across sectors found that, on average, firms lose 6.6 percent of annual sales to electrical outages.[61] States have created special economic zones and biotech parks that offer tax concessions and access to good infrastructure and that act as a one-stop shop for public permits. Firms said they value these spaces, but some stressed that plots in these areas are limited and that newcomers cannot easily purchase space to establish research facilities.

Conclusions

The policies and services that support biomedical innovation in India are growing and will continue to improve. However, the deficiencies that exist today, particularly in human resources, regulation, financing, and infrastructure, present significant obstacles for developing new vaccines, drugs, and diagnostics. Although the government is investing in infrastructure and working on policy reforms, at the current pace, it will take years for the benefits of these changes to have an impact. Without a supportive environment, firms will struggle to build R&D capacity, constraining both industrial competitiveness and the development of needed health technologies.

Strengthening these enabling factors will not, of course, guarantee that firms conduct R&D on the most badly needed technologies. As under the current industrial model, firms will continue to pursue the most profitable projects. The next three sections take a closer look at the vaccine, drug, and diagnostics industries in India, asking how they are contributing to neglected disease R&D and the specific barriers and opportunities for them to expand their role.

[60]World Economic Forum. (2011). *World Competitiveness Report, 2011–2012* (Geneva: World Economic Forum).

[61]International Finance Corporation. (2006). India Enterprise Survey. Available at: http://enterprisesurveys.org/Data/ExploreEconomies/2006/india.

CHAPTER 3
VACCINES

3

India has established a reputation as an important global supplier of high-quality, low-cost vaccines, and the technological sophistication of its vaccine industry is growing.

This section will examine its potential to contribute to the development of needed new vaccines for developing countries.

New Vaccine Needs in Low- and Middle-Income Countries

Most children in developing countries now receive a set of basic vaccines, including the six vaccines included in the original World Health Organization (WHO) Expanded Programme on Immunization (EPI)—tetanus, diphtheria, pertussis, measles, polio, and tuberculosis—as well as hepatitis B (Hep B) and *Haemophilus influenza* type B (Hib). Globally, coverage of basic childhood immunization programs now exceeds 80 percent.[62] Two important newer vaccines—against streptococcal pneumonia and rotavirus—are now being introduced in many countries, with financial help from the Global Alliance for Vaccines and Immunization (GAVI).[63]

But there are no licensed vaccines against several of the most important infectious diseases affecting poor countries, including HIV and malaria but also hepatitis C, dengue, parasitic diseases such as hookworm, leishmaniasis, and Chagas disease, and many others. Vaccine candidates for malaria and dengue are in advanced clinical trials, but for most of the others, work is still at early stages. For other diseases, including TB, typhoid, and cholera, existing vaccines are insufficiently effective or have other important drawbacks. For example, the only available type of TB vaccine (BCG) protects children only partially and adults not at all. Many vaccines, originally developed for high-income countries, are not well suited to poor countries: heat-stable (and freezing-stable) presentations, more convenient dosing schedules, and oral versions could all increase the reach and impact of immunization programs.[64]

Finally, many of the newer vaccines, particularly the pneumococcal-conjugate, rotavirus, and human papillomavirus (HPV) vaccines, are too expensive for low-income and many middle-income countries to purchase without help. Although GAVI is subsidizing these vaccines for the poorest countries, many middle-income countries are not eligible for GAVI support, and others, including India, are expected to become ineligible in the next few years. High prices also strain GAVI's resources. The entry of new suppliers, particularly those with experience in high-volume, low-cost production, could drive down prices of these vaccines. These "follow-on" vaccines are not

[62]WHO/UNICEF. (2012). *Global Immunization Data*. Available at: http://www.who.int/immunization_monitoring/Global_Immunization_Data.pdf. See also Lim, S. S., Stein, D. B., Charrow, A., & Murray, C. J. L. (2008). Tracking progress towards universal childhood immunisation and the impact of global initiatives: A systematic analysis of three-dose diphtheria, tetanus, and pertussis immunisation coverage. Lancet 372(9655): 2031–46.

[63]GAVI subsidizes the purchase of a set of new and underused vaccines for countries with per capita income below about $1,500.

[64]Médecins Sans Frontières. (2012). *The Right Shot: Extending the Reach of Affordable and Adapted Vaccines* (New York: Médecins Sans Frontières).

Box 3.1: Generic drugs, biosimilars, and "follow-on" vaccines

Regulatory agencies offer simplified processes for approving new suppliers of already licensed small-molecule drugs. Producers of such "generic" drugs must demonstrate that their products are chemically identical to the approved drugs, manufactured safely, and taken up by the body to an equivalent degree, but they do not have to independently demonstrate safety and efficacy. As a consequence, the cost of bringing a generic drug to market is far lower than the cost of developing a new medicine. However, it is not in general possible to demonstrate molecular identity for biological drugs ("biologics")—medicines consisting of large biological molecules, typically proteins, and produced in living systems. Regulators are only now introducing processes for approving follow-on versions ("biosimilars") of these increasingly popular drugs; these processes represent a compromise between the requirements for generic drugs and procedures for entirely new drugs.

Although vaccines are also biologics, they are generally even more complex than biologic drugs and are not covered by these new procedures. There is thus no such thing as a generic vaccine. Even vaccines based as closely as possible on licensed products must prove safety and efficacy in clinical trials, although for many well-established classes of vaccines these trials can be smaller than the trials used to license the original vaccine.

Source: Corbel, M.J. & Cortes-Castillo, M.A (2009) Vaccines and biosimilarity: a solution or a problem Expert Rev. Vaccines 8(10): 1439-49.

generics (see Box 3.1) and require meaningful R&D. We therefore include this kind of vaccine development in our analysis, along with the development of new, first-in-class vaccines.

Industry Overview

Vaccine development and production in India date back to the late nineteenth century, when vaccines against plague and cholera were developed at Indian research institutes.[65] Although vaccine research subsequently lagged, indigenous manufacturers have long supplied most of the basic vaccines required by India's public-sector immunization program.

Until relatively recently, vaccines for public-sector use were provided primarily by state-owned manufacturers that had been established or transferred to public ownership since independence. However, in recent decades, many public producers were shut down, culminating in the closure of three important suppliers in 2008.[66] Beginning with Serum Institute of India, privately owned vaccine companies began to play a more important role in the 1990s. In recent years, private Indian firms have moved into export markets and become important suppliers to UNICEF, to the Pan American Health Organization (PAHO) Revolving Fund, and to some other middle-income countries (see Section 4). To enter these markets, these producers have had to upgrade their manufacturing facilities to win WHO prequalification, a certification required for purchase by UN agencies and most developing countries. Five Indian manufacturers currently have at least one prequalified vaccine.[67] No Indian vaccines are approved for marketing in the United States or Europe.

Indian manufacturers initially focused on the so-called traditional vaccines included in the original EPI. But beginning with the launch in 1997 by Shantha Biotechnics of a hepatitis B vaccine based on recombinant DNA technology, Indian firms moved into newer and more sophisticated types of vaccines. Several firms have achieved, or are seeking, prequalification of pentavalent combination vaccines, which include Hep B and Hib as well as diphtheria, tetanus,

[65]Madhavi, Y. (2005). Vaccine policy in India. *PLoS Med* 2(5): e127.

[66]Madhavi (2005). Srinivasan, V. (2009). Certification, corruption, and cost: The fight for a vaccine production policy. *Infochange*. Available at: infochangeindia.org/public-health/analysis/certification-corruption-and-cost-the-fight-for-a-vaccine-production-policy.html.

[67]The firms with prequalified vaccines are Serum Institute, Shantha Biotech, Biological E, Haffkine, and Zydus Cadila. Two additional manufacturers—Panacea Biotec and Bharat Biotech—had prequalified vaccines as recently as 2011 but lost the certification. The list of prequalified vaccines can be found at www.who.int/immunization_standards/vaccine_quality/PQ_vaccine_list_en/en/index.html.

Table 3.1. Leading Indian vaccine manufacturers

	Revenue 2010–11 (US$ millions)*	Selected licensed vaccines (bold if WHO PQ)**	Selected vaccines in pipeline (bold if in trials)***	Ownership
Serum Institute of India	226	**BCG, DTP, MMR, Penta, Men. A conj.**, H1N1 Flu	**Rota**, Pneumo, **Seasonal Flu, Rabies**, Acellular Pertussis, HPV	Private
Panacea Biotec	201	Heb B, Penta, OPV, IPV	Dengue, **anthrax**, JE, **Flu**	Publicly traded
Bharat Biotech	65	Hep B, Penta, OPV, rabies, H1N1 flu, Typhoid	**Rota, JE, Typhoid conj., malaria**, HPV, Chikungunya	Private
Indian Immunologicals	62	Rabies, MMR, Hep B	HPV, Chikungunya, JE	State-owned
Shantha Biotech	59	**Hep B, Tetanus, Cholera**	**Rota**, Penta, Hexavalent with IPV, HPV, Typhoid conj.,	MNC -owned
Biological E	55	**Penta, Tetanus**, DTP, IPV, JE	Men. conj., IPV combinations	Private

Sources: *Biospectrum/ABLE 2011 Survey except Biological E: Mahima Datla, Senior Vice President, personal communication to PW

**Company websites, WHO prequalification list

***Company websites, interviews, press reports, and Ganguly, N. K., Mukhopadhyay, B., Gupta, S. S., & Bharati, K. (2010). Mapping of Health Products R&D Landscape for Infectious Tropical Diseases in India. (National Institute of Immunology, New Delhi, India).

Notes: PQ: prequalified; DTP: diphtheria-tetanus-pertussis combination; MMR: measles-mumps-rubella combination; Penta: pentavalent; Men. A conj.: Meningitis A conjugate; Flu: influenza; Rota: rotavirus; Pneumo: pneumonia: OPV: oral polio vaccine; IPV: inactivated polio vaccine; JE: Japanese encephalitis; HPV: human papillomavirus; MNC: multinational corporation

and pertussis. These vaccines are among the most important purchased by GAVI.[68]

In addition to Serum and Shantha, Panacea Biotec, Biological E. Limited, and Bharat Biotech International are important private-sector vaccine producers. Zydus Cadila, a large drug company, is also moving into vaccines. Although state-owned manufacturers continue to supply basic vaccines to public immunization programs, they have lagged behind private firms in technological sophistication and innovation in recent years. One exception is Indian Immunologicals, a long-time producer of veterinary vaccines, which is owned by the National Dairy Development Board. This firm has developed a human rabies vaccines and has a number of other human vaccines in its portfolio and more in its development pipeline. Table 3.1 provides information on the revenues and portfolios of the leading firms.

Definitive figures on the size of the Indian vaccine industry are hard to come by—in part because most of the leading firms are privately held. The most widely cited source, an annual survey of firms, estimated total human vaccine sales by Indian manufacturers in at $417 million in 2010.[69] Another

[68]In a major setback for the Indian vaccine industry, as well as for GAVI, two Indian companies have lost prequalification for their pentavalent vaccines since 2010.

[69]Biospectrum-ABLE survey 2010, cited in PricewaterhouseCoopers. (2011). India Pharma Inc.: *Capitalizing on India's Growth Potential*. Available at: www.pwc.com/in/en/publications/publications-2011/capitalising-on-indias-growth-potential.jhtml.

source put revenues at $655 million.[70] The largest India firm, Serum Institute, brought in $226 million in 2011, followed by Panacea Biotec, with $201 million in revenues.[71]

Shantha Biotech was purchased by Sanofi Aventis in 2009. This sale, as well as the recent acquisition by foreign companies of several Indian drug firms, raised concerns that control by multinationals could endanger the special role that Indian firms have played in supplying affordable drugs and vaccines.[72] So far, however, this has been the only high-profile foreign acquisition of an Indian vaccine firm, and it is probably too early to tell what it will mean for Shantha or for the industry. Shantha is apparently continuing its major vaccine development projects aimed at developing-country markets.[73]

Markets and Business Models

The Indian government remains an important buyer for some Indian companies, though the private sector and export markets are increasingly important. In particular, the UNICEF, PAHO, and GAVI markets have been important sources of revenue for those companies that have had prequalified vaccines, especially Serum Institute, Haffkine Institute, Bharat, and Panacea.[74]

According to the 2010 industry survey, domestic sales accounted for $238 million, or 57 percent of revenues, to Indian manufacturers in 2010, while exports brought in $179 million.

The Indian Public Sector

The Indian public-sector market is large in volume—the annual birth cohort of 27 million is the largest in the world—but prices are low, and the national immunization program has been slow to adopt newer vaccines, including some that are widely used in other low- and middle-income countries and are included in GAVI's portfolio. Currently, only the six original EPI vaccines plus Hep B are included in the Ministry of Health and Family Welfare's Universal Immunization Program (UIP) for all regions; however, pentavalent has been introduced in two states, and Japanese encephalitis is used in some areas. Other vaccines, including influenza vaccines, have been purchased in response to epidemics, and rabies vaccines are important at the state level. In contrast, the great majority of GAVI-eligible countries have now adopted pentavalent vaccines for all children, and many plan to introduce the rotavirus and pneumococcal-conjugate vaccines. Since the Indian government has a history of introducing vaccines only when they are available from domestic producers, it is possible that India will adopt these newer vaccines once the Indian candidates now in development reach the market.

Immunization coverage in India has also been low: 72 percent in 2010 according to WHO-UNICEF estimates, but only 44 percent according to survey data from somewhat earlier.[75] Coverage is particularly low in certain northern states. According to one study, the UIP spends only about $20 million per year on the six basic vaccines, or less than $1 per eligible child.[76]

[70]India's vaccine manufacturing set to soar to $800 million: Professor Steven Myint. *India Post*, May 16, 2011, quoting Steven Myint of Green Signal Bio Pharma.

[71]BioSpectrum. (2011). *BioSpectrum-ABLE Biotech Industry Survey 2011*. (India). These figures include some revenues from sales of other products.

[72]"Activists decry India-EU IPR talks." *Times of India*, October 6, 2010. Silverman, E. (2011). India may cap foreign investment in Pharma. *Pharmalot* (September 27). Available at: www.pharmalot.com/2011/09/india-may-cap-on-foreign-investment-in-pharma/.

[73]Interview with Harish Iyer, CEO of Shantha, May 29, 2012.

[74]Panacea and Bharat have recently lost prequalification for important vaccines, which will greatly reduce their export revenues, at least in the short run.

[75]WHO-UNICEF estimates are available at http://apps.who.int/immunization_monitoring/en/globalsummary/timeseries/tswucoveragedtp3.htm. National Family Health Survey data are available at http://www.nfhsindia.org/factsheet.shtml.

[76]Madhavi, Y., et al. (2010). Evidence-based national vaccine policy. *Indian J Med Res 131:* 617–28.

Another source estimates the total public-sector vaccine market at $130 million, or about half of the total Indian market. Much of the discrepancy is accounted for by polio vaccines for the elimination campaign, influenza vaccines, and rabies vaccines bought by state governments.[77]

Historically, the Indian government relied mostly on state-owned firms for basic vaccines; the role of for-profit firms, including Indian ones, remains controversial. Following a WHO report of quality-control deficiencies, the government shut down three important public producers in 2008; however, the government of India (GOI) has subsequently announced that it will invest in reviving these producers and bringing them to international standards.[78] These suppliers are not currently capable of producing newer kinds of vaccines, such as Hep B, Hib, or the pentavalent combination. There is also currently no public-sector supplier of measles vaccine.

Sales to the Indian public sector remain important to most Indian firms. In interviews, however, several firms explained that uncertainty about adoption decisions, as well as low prices, deter them from relying on this market in making decisions about investment in new vaccines. One firm added that all-or-nothing tenders compounded the uncertainty associated with public-sector procurement. A leading firm told us that they do not plan on Indian public-sector sales, but try to build sufficient capacity to be able to supply the government if needed.

Private-Sector Markets

India's private-sector market is large and growing. One source put sales at $140 million, and others considerably higher; McKinsey projects that it could grow by as much as 20 percent a year.[79] In addition to markets for rabies, basic childhood vaccines, and influenza, there are growing markets for more advanced combination vaccines, as well as for vaccines not included in the public-sector programs (and, in many cases, only available from multinationals), such as chickenpox, rotavirus, pneumococcal-conjugate, and HPV. Some Indian firms, notably Serum Institute, also sell to the private sector outside of India. In general, however, Indian firms have not made large investments in international marketing or in establishing offices outside India.

The Indian vaccine market remains small compared with U.S. and European markets—at $270 million, it represents less than 2 percent of a global market estimated at $23 billion in 2010.[80] However, the Indian market it is projected to grow rapidly, along with other emerging markets, such as China and Brazil.

UNICEF, GAVI, and PAHO Markets

Those Indian firms that have achieved WHO prequalification have benefited greatly from the two major international pooled procurement schemes—UNICEF Supply Division and PAHO's Revolving Fund. These mechanisms, which buy vaccines on behalf of most developing countries, have opened large and relatively transparent markets to these suppliers.[81] The Indian firms, and to a lesser extent suppliers from other developing countries, have helped ensure continued supply of basic vaccines and brought down prices for some of the newer vaccines purchased by UNICEF with financing from GAVI. In 2008, 53 percent of the vaccines purchased with GAVI funds were

[77]Dash, S. K. (2011). Understanding the Indian conundrum and developing strategies to enhance its vaccines market. Presentation at World Vaccine Congress Asia (Singapore, June 8–11, 2010). Available at: www.slideshare.net/Shubhendu_dash/indian-vaccine-scenario-by-s-k-dash.

[78]Jayaranam, K. (2010). "Universal" immunizations get boost in India. *Nature Medicine 16*(5): 497.

[79]Dash, S. (2011). The collective voice of the Indian biotechnology sector. Presentation of the Association of Biotechnology Led Enterprises. Bhadoria, V., Bhajanka, A., Chakraborty, K., & Mitra, P. (2010). *India Pharma 2020: Propelling Access and Acceptance, and Realizing True Potential*. McKinsey & Company report on Pharmaceutical and Medical Products Practice.

[80]Martin, A. (2011). GSK vaccines in 2011.Presentation at Citi's Seminar on Vaccines in Emerging Markets (London, UK, March 23).

[81]For an overview of these mechanisms, see International AIDS Vaccine Initiative. (2008). *Procurement and Pricing of New Vaccines for Developing Countries* (IAVI Policy Brief). Available at: www.iavi.org/Information-Center/Publications/Pages/Procurement-and-Pricing-of-New-Vaccines-for-Developing-Countries.aspx.

supplied by emerging market firms, most of them Indian.[82] (This fraction may fall, at least temporarily, as rotavirus and pneumococcal vaccines currently supplied only by multinationals become a bigger share of the GAVI market.) In 2010, Indian firms sold $220 million of vaccines to UNICEF, or 29 percent of $759 million in total purchases.[83] UNICEF's purchases include polio and other basic childhood vaccines as well as GAVI-financed vaccines.

UNICEF estimates that it purchases 40 percent of global vaccine doses, though these purchases account for only 5 percent of the world vaccine market, because most are relatively simple vaccines and because UNICEF generally pays much lower prices than public or private buyers in high-income countries.[84] The PAHO Revolving Fund, which procures on behalf of many Latin America and Caribbean countries, purchased vaccines worth about $500 million in 2010.[85] The Revolving Fund, which serves mostly middle-income countries, now pays higher prices than UNICEF/GAVI for some newer vaccines. But PAHO and UNICEF prices for vaccines supplied by Indian firms are probably similar.[86]

Although UNICEF and PAHO prices are low by rich-country standards, these markets have nonetheless been profitable for Indian firms. Several firms stated that these exports have been an essential source of funds for R&D. Perhaps at least as important, these exports have provided a powerful incentive to upgrade manufacturing practices and have helped bring firms into greater contact with international partners and sources of technology. For example, the Gates Foundation's objective of ensuring supply and reducing costs to GAVI underlies its assistance to Serum Institute's and Bharat Biotech's rotavirus development projects (see the case study at the end of this section).

Other Export Markets

Almost all low-income and many middle-income countries buy vaccines for public-sector immunization programs through UNICEF or PAHO. But other middle-income countries, which in general pay higher prices than UNICEF, represent another potentially important market for Indian firms. According to Serum Institute, its products are used in 140 countries. Most firms have not made the investment in marketing and local offices necessary to break into these markets on a large scale.

We have not been able to find data on the overall breakdown of vaccine sales by Indian manufacturers among the various domestic and export markets. Serum reported that in 2008, exports—to UNICEF and PAHO and directly to middle-income countries—accounted for 85 percent of its revenues.[87] In contrast, other firms, such as Biological E. Limited, rely primarily on the Indian market.[88]

So far no vaccine produced in India has won regulatory approval in either the United States or the European Union—this is an important difference between the vaccine and drug industries. Serum, in particular, stated that winning access to these markets is a goal, which may be one rationale for its recent partnership with Merck to develop a new pneumococcal-conjugate vaccine that would be sold in high-income as well as developing countries.[89]

[82]GAVI. (2010). *Financing Country Demand for Life-Saving Vaccines* [fact sheet] (Geneva: GAVI Alliance).

[83]UNICEF. (2011). *Supply Annual Report 2010*. Available at: www.unicef.org/publications/index_59002.html.

[84]International AIDS Vaccine Initiative. (2008). *Procurement and Pricing of New Vaccines for Developing Countries* (IAVI Policy Brief). Available at: www.iavi.org/Information-Center/Publications/Pages/Procurement-and-Pricing-of-New-Vaccines-for-Developing-Countries.aspx.

[85]PAHO. (2011). PAHO Revolving Fund: Vaccine and syringe prices, 2011. *Immunization Newsletter 33:* 4–7.

[86]UNICEF vaccine prices can be found at www.unicef.org/supply/index_57476.html. PAHO provides only weighted average prices, which are published annually in their *Immunization Newsletter*.

[87]Mahalingam, T. V. (2008). Meet India's biotech giant. *Business Today* (August 24).

[88]Interview with Mahima Datla of Biological E, August 29, 2011.

[89]Merck. (2011, August 3). Merck and Serum Institute announce collaboration to develop and expand global access to pneumococcal conjugate vaccine (PCV) [press release].

Although Indian firms are trying to build their R&D capacity, their business model remains focused primarily on high-volume, low-cost production of existing vaccine types.

Perception of Neglected Disease Products

All the vaccines currently produced or in development by Indian firms are against infectious diseases of public health importance in low- and middle-income countries. Although this orientation originates with the historic focus of these firms on supplying the Indian immunization program, it is reinforced by two important features of the industry.

First, vaccines are historically against infectious diseases (though there is now great interest in the possibility of cancer vaccines), and almost all infectious diseases are either global or primarily a problem in developing countries. Second, Indian firms have not yet gained access to the U.S. or European markets. As a result, in cases where different types of vaccines against the same disease are used in high-income and developing countries, Indian firms have focused to date on products used in India or procured by UNICEF. For example, high-income countries use the acellular (as opposed to the whole-cell) pertussis vaccine and the inactivated (rather than live attenuated) polio vaccine. This may change, as private-sector markets in India for the more expensive types of vaccines grow and as UNICEF contemplates a shift to different vaccines.

Although the vaccines produced by Indian firms are intended for markets in developing countries, they are not always the same as those currently used in India's own national immunization program. Some Indian critics of industry have charged that the focus of private-sector producers on more expensive vaccines such as pentavalent, coupled with the closure of public-sector suppliers, has led to a shortage of basic vaccines needed by the public sector.[90] Moreover, critics have asserted that the inclusion of vaccines against Hep B and Hib in the Indian program is not justified by disease burden and is being promoted to serve the interest of domestic and international vaccine companies.[91] These assertions have been rebutted by others, and an expert committee set up to review the decision has supported introduction of pentavalent.[92]

The vaccines in the R&D portfolios of the Indian firms remain intended for markets in low- and middle-income countries, with the possible exception of the 15-valent pneumococcal-conjugate vaccine that Serum is developing in collaboration with Merck.

In most cases (see discussion below), vaccines in development are variants of existing vaccines, which the Indian firms are likely to sell at lower prices than existing suppliers, thus benefiting developing countries by making these vaccines more affordable. Some Indian firms are also working on vaccines for what would generally be considered neglected diseases, including Japanese encephalitis and malaria, and even chikungunya and typhoid. Several firms told us that they could consider products that had only modest markets as long as they thought they would be able to at least cover costs; this attitude may reflect the freedom conferred by being privately held (as opposed to publically traded) or, in the case of Indian Immunologicals, state-owned.[93] It is also possible that some firms underestimate R&D costs and risks, as most still have little experience with developing truly new products.

[90]Varshney, V. (2009). Get your own vaccine. *Down to Earth*. Available at: www.downtoearth.org.in/content/get-your-own-vaccine. Madhavi, Y., et al. (2010). Evidence-based national vaccine policy. *Indian J Med Res 131:* 617–28.

[91]Madhavi, Y., et al. (2010). Madhavi, Y. (2005). Vaccine policy in India. *PLoS Med 2*(5): e127.

[92]Nair, H., Hazarika, I., & Patwari, A. (2011). A roller-coaster ride: Introduction of pentavalent vaccine in India. *Journal of Global Health 1*(1): 32–25.

[93]Although Indian Immunologicals is wholly owned by the National Dairy Board, it has considerable freedom to set its own R&D priorities and to operate in some ways like a private company.

All firms agreed, however, that there were some needed products for which the commercial prospects were so poor that they could not take up the necessary R&D, at least not without outside financing.[94] One firm mentioned cholera and typhoid, while another put chikungunya in this category. Moreover, even in cases where firms have early-stage programs against very neglected diseases, it is not clear how they would finance late-stage development, and it is likely that they would require help from the Indian government or international donors. Thus, Indian firms remain focused on vaccines used or needed by developing countries, including many that do not interest the multinational companies. But they cannot or will not work on some products without additional funding or other incentives.

R&D Capacity and Activity

Vaccine R&D in India is expanding in both the public and the private sectors. A recent report from the National Institute of Immunology provides a comprehensive survey of vaccine, drug and diagnostic R&D projects in both the public and private sectors.[95] In the public sector, university research has traditionally been weak, and the most advanced work takes place at public research institutes, as well as at the state-owned producer Indian Immunologicals. Among the neglected disease vaccine projects that have reached clinical trials with industrial partners are a malaria vaccine developed at the International Center for Genetic Engineering and Biotechnology (ICGEB) in Delhi, an anthrax vaccine developed at Jawaharlal Nehru University, and the rotavirus vaccine candidate discovered at the All India Institute of Medical Sciences and now in Phase 3 trials (see the case study). But these are exceptions: despite the high quality of science at some public institutes, most vaccines that have been successfully commercialized in India, and the majority of candidates in the development pipeline, are based on technology obtained from abroad.[96]

In industry, a growing number of vaccines are in development, including vaccines against rotavirus, Japanese encephalitis, streptococcal pneumonia, bacterial meningitis, rabies, HPV, typhoid, malaria, hepatitis A, chikungunya, influenza, and polio (see Table 3.1).[97] The majority of these vaccines are variants of existing vaccines, but several, including the malaria and chikungunya candidates as well as the typhoid conjugate and some of the HPV vaccines, would be first-in-class or would represent new strategies. Others involve significant process innovations. But bringing even relatively straightforward vaccines to market involves substantial investment in design, process development, formulation, and, in some cases, clinical trials. Most projects are still at early stages and it is difficult to assess their viability.

From a global perspective, the most important Indian vaccines in development are probably the rotavirus, pneumococcal conjugate, and HPV vaccines, which could offer lower-priced alternatives to vaccines that are currently only available from multinational firms, as well as, perhaps, the prospect of better or more locally adapted vaccines. The rotavirus vaccines are in advanced development, whereas the pneumococcal and HPV candidates are still at preclinical stages. An effective malaria vaccine would be a breakthrough, but the history of malaria vaccine development suggests that these candidates face long odds.

[94]Executives from Serum Institute, Shantha Biotech, Bharat Biotech, Indian Immunologicals, Biological E, and Gennova (a unit of Emcure working on a number of new vaccines) were interviewed for this report. See Annex III.

[95]Ganguly, N. K., Mukhopadhyay, B., Gupta, S. S., and Bharati, K. (2010). *Mapping of Health Products R&D Landscape for Infectious Tropical Diseases in India*. (National Institute of Immunology, New Delhi, India).

[96]This statement is based primarily on our interviews with industry executives. But it is consistent with published studies (see notes to subsection on access to technology as a barrier to R&D later in this section).

[97]Information on company pipelines comes from our interviews with firms and company websites, from press reports, from the Ganguly et al. (2010) report, and from peer-reviewed articles, including Milstien, J. B., & Kaddar, M. (2010). The role of emerging manufacturers in access to innovative vaccines of public health importance. *Vaccine 28*(9): 2115–21; and Frew, S. E., Rezaie, R., Sammut, S. M., Ray, M., Daar, A. S., & Singer, P. A. (2007). India's health biotech sector at a crossroads. *Nat Biotechnol 25*(4): 403–17.

The consensus of experts interviewed for this study, including scientists involved in collaborations with Indian partners, is that R&D capacity in the Indian vaccine industry has grown substantially, but that important gaps persist. On the one hand, the leading firms have demonstrated the ability to bring follow-on vaccines to market; to carry out incremental innovation in presentations and formulation; and to develop high-quality, low-cost production processes. On the other hand, these firms still have little experience with the large-scale, community-based trials necessary to demonstrate efficacy for first-in-class vaccines, and they are still well behind the leading multinational firms in sophisticated vaccine discovery. Moreover, there appears to be a significant drop in R&D capacity behind the leading firms, in particular Serum and Shantha.

It is worth noting that most of the more ambitious vaccine R&D projects in India are receiving support from international partners, notably the Gates Foundation. The Program for Appropriate Technology in Health (PATH), with funding from the Gates Foundation, is supporting both Serum Institute's and Bharat's rotavirus programs, as well as Serum's pneumococcal-conjugate vaccine. PATH support to these projects has included not only substantial financing, especially for clinical trials, but also technical assistance in various aspects of development. The International Vaccine Institute, based in South Korea, has worked with Shantha on cholera and typhoid vaccines, while the European Malaria Vaccine Initiative has supported ICGEB's malaria program. The Indo-U.S. Vaccine Action Program, a 20-year collaboration between the U.S. and Indian governments, has supported a number of vaccine development projects in India.

The Meningitis Vaccine Project (MVP), a largely Gates Foundation–funded initiative that led to the development of a meningitis A conjugate vaccine for the African meningitis belt, is an example of a successful partnership between international donors and an Indian vaccine company.[98] The MVP funded and organized clinical trials in India and Africa and facilitated the transfer of a key conjugation technology from the U.S. FDA to Serum Institute. Serum, in turn, invested its own resources in the project and committed to supplying the vaccine at about $0.50 per dose. This price is almost certainly lower than could have been obtained from a multinational firm, which would not benefit from access to this technology and would not find the market for the resulting vaccine commercially attractive. The new vaccine has now been rolled out in at least six countries and is already having a big impact on disease. It is worth noting that GAVI funding for at least the initial catch-up campaigns in Africa was important to this project too, as even at this relatively low price the impoverished countries would have represented a very uncertain market.

This collaboration could be a model for some other vaccines, though it is probably most applicable to relatively well-understood types of vaccines based on technologies available in the public sector.

R&D Spending

Data on R&D spending by Indian firms are hard to come by because most firms are privately held. Available estimates suggest that this spending remains relatively low as a percentage of sales. For example, Panacea (the only one of the leading vaccine manufacturers that is publicly traded) reports that it spent about $17 million on R&D in 2011, corresponding to 7.5 percent of turnover. Even the largest Indian vaccine company probably has fewer than 100 scientists working on new products.[99] By comparison, GlaxoSmithKline (GSK) spent $6.2 billion on R&D in 2009 (on both vaccine and drug development) and claims to have approximately 1,600 scientists involved in developing new vaccines.[100] The

[98]Frasch, C., Preziosi, M. P., & Laforce, F. M. (2012). Development of a group A meningococcal conjugate vaccine, MenAfriVac. *Hum Vaccin Immunother 8*(6) [Epub ahead of print].

[99]Interview with Serum Institute, January 13, 2012.

[100]GlaxoSmithKline annual report 2010.

pharmaceutical giants typically spend more than 15 percent of their much greater revenues on R&D.

This comparison illustrates an important point: despite producing a large share of the world's vaccine doses, Indian firms remain, in many respects, small players relative to the multinationals, including in R&D resources. One consequence of this difference in scale is that Indian firms probably do not have the resources to pay for the most expensive kinds of clinical trials, such as phase 3 rotavirus trials, without help. Another is that they have much less scope for spreading R&D risk across a portfolio of projects, which may in turn limit their ability to raise funds for R&D from private investors and their willingness to take on expensive and risky projects.

The imbalance in R&D spending between Indian firms and Western multinationals is partially mitigated by lower R&D costs. Firms and outside experts agreed that many specific elements of R&D cost are lower in India than in the U.S. or Europe, but that this advantage is eroding. One of the most important cost advantages has been in the salaries of skilled personnel, but with rising incomes in India and increasing international movement of professionals, the difference in salaries is shrinking. Brick-and-mortar construction is considerably cheaper in India, but sophisticated equipment is often more expensive as a result of import dues and shipping costs, as are basic infrastructure costs, such as electricity and water. Clinical trials are cheaper, because of lower personnel costs, greater ease of recruiting patients, and perhaps less stringent regulation, but this difference is apparently shrinking as well. Bharat estimates that its rotavirus trial is costing 20–30 percent less per patient than those done by GSK and Merck.[101]

The real cost of doing R&D in one setting relative to another cannot be fully captured by this kind of breakdown, however, as it does not take into account the quality of the work and, ultimately, the chances of success. Remaining gaps in skills, experience, and access to technology may make some kinds of R&D impossible or impractical in India; in other cases, slower progress or lower probability of success may negate lower costs.

Sources of R&D Funding

The privately held vaccine firms that we interviewed relied to a great extent on their own resources rather than on outside investors to finance R&D. Bharat and Serum are also receiving substantial support from the Gates Foundation for their late-stage rotavirus projects. Several firms have also benefited from Indian government grants and loans for specific projects, especially from DBT and from the Council of Scientific and Industrial Research's (CSIR's) New Millennium Indian Technology Leadership Initiative (NMITLI) program (Annex 1).

The strategy of financing R&D from revenues apparently works well for those companies that have thrived in export markets, though it undoubtedly limits the number and scale of projects they can undertake. This strategy—and private ownership more broadly—may give some firms greater flexibility in setting R&D priorities than a publicly traded firm responding to stockholders' preferences would have. For example, the head of R&D at Serum told us that he has no fixed budget to work with, but asks his chairman for the necessary resources for particular projects.[102]

R&D Obstacles

What are the most important obstacles to the development of needed new vaccines in India? Our findings are based in large part on interviews with vaccine companies, though we return to the broader innovation system later in this section. Many of the obstacles cited by vaccine company executives are similar to those cited by drug and diagnostic executives (see Section 2). We emphasize here those issues specific or particularly important to vaccine R&D.

[101] Interview with Bharat Biotech, August 29, 2012.

[102] Interview with Serum Institute, January 13, 2012.

Financing

Access to financing for R&D was cited as an important obstacle by only one of the six firms interviewed for this study. As discussed earlier, however, it is likely that reliance on internal sources limits the number and size of R&D projects, and most or all firms would almost certainly need external resources to carry out large efficacy trials for new vaccines. Private sources of capital would probably be ill-suited for most neglected disease projects, which cannot offer returns that are competitive with those promised by lower-risk investment elsewhere in India's fast-growing economy, including the production of generic drugs for export to the U.S. and Europe.

Skilled Personnel

Indian vaccine firms offered mixed—and sometimes conflicting—views on the extent to which a shortage of people with the needed skills was a problem. These views were similar to those of executives in the drugs and diagnostics industries, as summarized in Section 2.

Intellectual Property and Access to Technology

Technologies both for vaccines currently produced in India and for those in the development pipelines of Indian vaccine firms were generally obtained from abroad, although Indian firms may have made significant modifications to production processes.[103] In many cases, the source was the WHO, the public sector, or a philanthropic entity. For example, the Dutch National Vaccine Institute transferred technology for Hib production to several firms, using a conjugation technology first developed at the U.S. National Institutes of Health (NIH); Panacea's Hep B technology came from Cuba; the meningitis A conjugation technology came from the U.S. Food and Drug Administration (FDA); the rotavirus technology used by Serum and Shantha comes from the NIH; and the International Vaccine Institute (IVI) has facilitated the transfer of technology for cholera and typhoid vaccines to Shantha Biotech. In other cases, such as Biological E.'s Japanese encephalitis vaccine and the expression system for Serum's HPV candidate, technologies have been acquired through deals with for-profit companies.[104] Serum has announced an ambitious collaboration with Merck on pneumococcal conjugate vaccines, while Novovax, an American biotech, is working with Cadila Pharmaceuticals on several vaccines based on virus-like particles.

Technology transfer between the Western public or philanthropic sector and firms in India or other developing countries potentially can serve both partners well. As illustrated by the MVP, international donors and technology holders benefit by having a partner with expertise—and commercial interest—in low-cost, high-volume production, while the developing-country company gains by building its technological base. The multinational firms, in contrast, have a different business model and in general have already mastered the relevant technologies and thus would gain little from this kind of partnership.

There are relatively few examples of commercialization by Indian firms of candidate vaccines originating in the Indian public sector, though Bharat's rotavirus vaccine is an important exception. Industry executives interviewed for this report did not see the domestic public sector as a promising source of new technologies for their purposes. This illustrates one of the gaps in India's broader innovation ecosystem.

Finally, although no Indian firm has developed a completely novel vaccine, some have developed their own versions of existing vaccines primarily through in-house efforts. The best-known example is Shantha Biotech's Hep B vaccine.[105] Thus, although the

[103]Milstien, J. B., Gaulé, P., & Kaddar, M. (2007). Access to vaccine technologies in developing countries; Brazil and India. *Vaccine 25*(44): 7610–19. WHO. (2011). *Increasing Access to Vaccines Through Technology Transfer and Local Production* (Geneva: World Health Organization).

[104]Milstien, J. B., Gaulé, P., & Kaddar, M. (2007). Access to vaccine technologies in developing countries; Brazil and India. *Vaccine 25*(44): 7610–19. Padmanabhan, S., Amin, T., Sampat, B., Cook-Deegan, R., & Chandrasekharan, S. (2010). Intellectual property, technology, and manufacture of low-cost HPV vaccines in India. *Nat Biotechnol 28*(7): 671–78.

[105]Chakma, J., Masum, H., Perampaladas, K., Heys, J., & Singer, P. A. (2010). India's billion-dollar biotech. *Nat Biotechnol 28*(8): 783.

leading Indian firms appear to have growing contacts with international sources of vaccine technology, their less-developed links to universities and biotechs, as well as their still modest capacity to develop new vaccine candidates in-house, leave them at a significant disadvantage relative to the multinationals in access to new technology.[106]

Traditionally, patents have not been considered a critical obstacle to vaccine development and production, because most patents have been on processes and because unpatented proprietary knowledge ("know-how") has been a more important barrier. The rate of patenting in vaccines has been increasing, however, and there has been concern that Indian firms would have difficulty producing new versions of some of the more recent vaccines in the wake of India's compliance with the Trade Related Aspects of Intellectual Property Rights (TRIPS) agreement in 2005. A study in 2007 concluded that patents were not yet major obstacles to firms in Indian and Brazil, but that securing freedom to operate was likely to become more difficult.[107] A study focused on HPV vaccines concluded there were probably no patents that would prevent Indian firms from developing these vaccines.[108]

Our interviews with firms confirmed that they devote resources to determining whether a particular path to a vaccine is open. One firm reported going to considerable lengths to find a way around patent barriers to HPV vaccines, while another told us that patents were an obstacle to a convenient formulation for one of its new vaccines. Thus, although patents may not constitute an insuperable block to vaccine development, as they often do to production of existing drugs, they can drive up costs and may deter Indian firms from pursuing some R&D avenues. A lack of capacity to adequately determine freedom to operate may be a more important problem than blocking patents themselves—Indian firms have a fraction of the in-house or contracted legal staff that multinational firms can deploy.

Regulatory Environment

Most interviewed firms cited regulatory policies and inefficiencies as important barriers to new vaccine development; one firm stated unequivocally that this was the most important obstacle to R&D. Firms cited several features of the current biotechnology regulatory environment:

- Excessive complexity, with many ministries and agencies (including the Ministry of Environment and Forests) involved in the regulation of research involving genetically modified organisms, imports, animal testing, clinical trials, production, marketing approval, and (in some cases) prices
- A lack of necessary expertise on the part of regulators, especially to assess novel technologies and products
- A focus on the mechanical application of rules rather than on finding solutions that could work for both industry and public welfare
- A lack of a consultative process, like that of the FDA, by which firms could receive guidance before submitting applications for regulatory approval

It is difficult to assess the validity of these claims or whether they point to a uniquely difficult regulatory environment in India—it is likely that firms everywhere have complaints about regulators—but some of the anecdotes did suggest serious deficiencies in regulatory capacity. It is also worth noting that the main complaints were not about the stringency of regulations per se, but rather about processes, attitudes, and competence.

[106]Milstien, J. B., & Kaddar, M. (2010). The role of emerging manufacturers in access to innovative vaccines of public health importance. *Vaccine 28*(9): 2115–21.

[107]Milstien, J. B., Gaulé, P., & Kaddar, M. (2007). Access to vaccine technologies in developing countries; Brazil and India. *Vaccine 25*(44): 7610–19.

[108]Padmanabhan, S., Amin, T., Sampat, B., Cook-Deegan, R., & Chandrasekharan, S. (2010). Intellectual property, technology, and manufacture of low-cost HPV vaccines in India. *Nat Biotechnol 28*(7): 671–78.

Lack of regulatory capacity cuts both ways, of course. There have been recent revelations about grossly inadequate oversight of clinical trials in India,[109] as well as problems with the approval of vaccine production by the Drugs Controller General of India (DCGI) as recently as 2007, which led to the temporary suspension by the WHO of new vaccine prequalification in India.

Conclusions

The Indian vaccine industry already supplies a large share of the basic vaccines used throughout the developing world and is now exporting more sophisticated Hep B– and Hib-containing vaccines as well. From a public health perspective, the industry contributes by making supply of these vaccines more secure and by bringing down prices. The capacity of many Indian firms to develop new vaccines is growing, which will allow the industry to play this same role for newer, more expensive vaccines, such as those against rotavirus, pneumococcal diseases, and HPV, by bringing to market cheaper versions of these vaccines. This promising scenario depends on the continued assurance of GAVI funding for vaccine purchase, financial support from both the GOI and international donors for expensive late-stage development, and technical support from overseas partners.

The contribution of the Indian vaccine industry is not limited to the supply of low-cost versions of vaccines developed by multinationals. It can also develop locally adapted vaccines, such as the meningitis A vaccine for Africa, or perhaps even entirely new vaccines against certain neglected diseases, and in many cases is interested in doing so on a commercial basis. The leading firms remain focused on products of public health importance in India and other developing countries and have been eager to work with international partners to develop these products. The MVP, the technology transfer agreements with IVI, and the rotavirus vaccine development partnerships demonstrate how these collaborations can serve the interests of both Indian manufacturers and global health donors. As the industry's R&D capacity remains limited in important ways, technical assistance of the kind that PATH, IVI, NIH, and others have provided will be crucial.

The most important barriers to new vaccine development by Indian firms are relatively undeveloped links to sources of new technology and vaccine candidates, both in the Indian public sector and abroad, lack of financing for expensive late-stage trials, lack of experience and personnel in certain areas, and (at least from industry's perspective) a burdensome and inefficient regulatory environment.

In the longer term, the capacity of Indian firms to develop important new vaccines will surely continue to grow. It is also possible, however, that the industry's contribution to public health objectives will be threatened by two developments: the transition of privately held or state-owned companies to publicly traded status or even acquisition by multinationals; and successful entry into lucrative U.S. or European markets. The latter development, though a happy one for Indian firms and perhaps for Indian industrial policy, could eventually turn these firms away from a focus on products used in (and needed by) low- and middle-income countries. But such a change in orientation does not seem imminent, and we conclude that Indian researchers and firms are currently able and ready to develop important new products for the developing world, with the help of the GOI and international partners.

[109]Yee, A. (2012). Regulation failing to keep up with India's trials boom. *Lancet 379*(9814): 397–98.

Case Study: Rotavirus Vaccines

Rotavirus infections are the most important cause of severe diarrhea in children, accounting for about 500,000 deaths every year and perhaps two million hospitalizations, mostly in sub-Saharan Africa and South Asia.[110] Rotavirus vaccines can be a powerful tool for reducing child mortality, and the development and introduction of these vaccines has been a public health priority for more than 20 years.

Two live, attenuated, oral vaccines are currently on the market internationally: GlaxoSmithKline's (GSK's) Rotarix and Merck's RotaTeq.[111] These vaccines have had a rapid and substantial impact in the countries where they have been introduced. In Mexico, for example, introduction of the vaccine in 2006–07 led to a 35 percent reduction in total diarrhea deaths by 2008–09.[112] These vaccines are still not in widespread use in the poorest countries, where their benefits would be greatest, but WHO has recommended their adoption in all countries, and GAVI has committed to supporting their purchase in eligible countries. Although GAVI support should greatly expand access to the two licensed vaccines, many experts believe that additional vaccines are needed, for the following four reasons.[113]

- **Efficacy.** The GSK and Merck vaccines were 85–100 percent effective in trials in the U.S. and Europe, but only 50–65 percent effective in high-child-mortality settings in Africa and South Asia.[114] Although the reason for this difference is not well understood, a vaccine with greater efficacy in these regions is clearly desirable.
- **Price.** GAVI subsidy will make rotavirus vaccines affordable to eligible countries. But the relatively high prices of the Merck and GSK vaccines may prevent adoption by some non-GAVI-eligible countries. The PAHO Revolving Fund paid $15 per course for these vaccines in 2011 (high-income countries pay much more.)[115] Moreover, even at the very discounted price of $5 per course recently announced by GAVI and GSK,[116] rotavirus vaccines would cost GAVI as much as $170 million by 2019.[117] The entry of new suppliers into the market is one of the most effective ways of reducing prices, because new suppliers may have lower production costs and because competition can push all suppliers to cut prices.
- **Supply and supply security.** GSK has committed to supplying its rotavirus vaccine to GAVI and has stated that it has sufficient capacity to meet global demand. But Merck has so far committed very few doses to this market. As recent supply disruptions for other vaccines attest, it is very risky to depend on a single supplier. Supply security is therefore a compelling argument for additional rotavirus manufacturers.
- **Adoption in India and Indonesia.** Finally, it is widely believed that India, and perhaps Indonesia, is much more likely to introduce rotavirus vaccines into its national program if it can purchase them from a domestic firm. Since India accounts for perhaps one-quarter of the global burden of rotavirus deaths, this is an additional reason for encouraging the development of an Indian rotavirus vaccine.

A number of rotavirus vaccine candidates are in active development, including at least two in India:

- Bharat Biotech, with several partners, is conducting a phase III trial of a vaccine based on a naturally attenuated rotavirus strain, 116E, isolated in a New Delhi hospital and subsequently developed as a vaccine candidate by Indian researchers in collaboration with scientists from the U.S. (NIH) and the Centers for Disease Control and Prevention (CDC). This vaccine could be licensed in India by 2014.

[110]Parashar, U. D., Gibson, C. J., Bresee, J. S., & Glass, R. I. (2006). Rotavirus and severe childhood diarrhea. *Emerg Infect Dis 12*(2): 304–06. Parashar, U. D., Hummelman, E. G., Bresee, J. S., Miller, M. A., & Glass, R. I. (2003). Global illness and deaths caused by rotavirus disease in children. *Emerg Infect Dis 9*(5): 565–72.

[111]Glass, R. I., Bresee, J. S., Turcios, R., Fischer, T. K., Parashar, U. D., & Steele, A. D. (2005). Rotavirus vaccines: Targeting the developing world. *J Infect Dis 192*(1): S160–66.

[112]Richardson, V., et al. (2010). Effect of rotavirus vaccination on death from childhood diarrhea in Mexico. *N Engl J Med 362*(4): 299–305.

[113]Ward, R. L., McNeal, M. N., & Steele, A. D. (2008). Why does the world need another rotavirus vaccine? *Ther Clin Risk Manag 4*(1): 49–63.

[114]WHO. (2009). Rotavirus vaccines: An update. *Wkly Epidemiol Rec 84*: 533–40.

[115]PAHO. (2011). PAHO Revolving Fund: Vaccine and syringe prices, 2011. *Immunization Newsletter 33*: 4–7.

[116]GAVI. (2012, April 10). GAVI Alliance secures lower price for rotavirus vaccine [press release].

[117]According to GAVI's strategic demand forecast, demand from GAVI-eligible countries will reach 34 million courses per year by 2019. See UNICEF Supply Division. (2012). Update on rotavirus vaccine. Presentation at the Industry Consultation Meeting (Copenhagen, Denmark, January 25–26).

Case Study: Rotavirus Vaccines (continued)

- Eight firms, including Serum, Shantha, Bharat, and Biological E. in India, licensed a rotavirus vaccine technology from the NIH.[118] Both Serum and Shantha are preparing for phase III trials of their candidates based on this technology. Brazilian and Chinese firms are also developing vaccines based on the NIH technology.
- Australian researchers and the Indonesian state-owned manufacturer Biopharma are developing a vaccine based on another naturally occurring strain.
- An American nonprofit, the International Medica Foundation, has completed a successful phase IIB trial in Ghana with Rotashield, a vaccine introduced in the U. S. by Wyeth in 1998 but withdrawn a year later after a small number of vaccinated children developed intussusception, a serious intestinal condition.
- Other researchers are exploring other vaccine concepts.[119] In particular, Baoming Jiang and his colleagues at the CDC are working on an inactivated, injected vaccine, which they hope will prove more effective than the oral vaccines in high-child-mortality settings.

Rotavirus vaccines are not as sophisticated or difficult to produce as, for example, the highly multivalent GSK and Pfizer pneumococcal-conjugate vaccines. The biggest challenge to bringing a new rotavirus vaccine to market is the need for large community trials with a clinical endpoint (lower incidence), because correlates of protection have not been established for rotavirus vaccines.[120] The current Bharat trial is following about 7,000 infants for two years. Such large trials are very expensive and require sophisticated planning and management.

To win U.S. FDA approval, GSK and Merck had to conduct even larger trials in order to demonstrate that their vaccines did not cause intussusception. One of GSK's trials included 63,000 children. Indian regulators have apparently agreed that the risk of intussusception from new rotavirus vaccines can be assessed after licensure through postmarketing surveillance.

The 116E candidate has benefited from both technical and financial support from DBT, the Indian Council of Medical Research, and the NIH (under the umbrella of the Indo-U.S. Vaccine Action Program), as well as from PATH (with funding from the Gates Foundation), both before and after Bharat was chosen as the industrial partner. PATH is also supporting the Serum candidate and is covering most of the costs of phase III trials for both vaccines, which will run to about $15–20 million in each case.[121]

Given the availability of the GSK and Merck vaccines, why are the Indian government, the U.S. NIH, and PATH investing so much in Indian rotavirus vaccines? A published review of the 116E program by leading U.S. and Indian participants emphasized the goal of a vaccine for India developed and produced in India, but states explicitly that the program's aim is to "expedite introduction of rotavirus vaccines in India," noting that an Indian vaccine might be more rapidly introduced into the routine immunization program.[122] The development of Indian vaccine R&D capacity has no doubt been an important consideration for the Indian government. Leaders of the PATH rotavirus work interviewed for this study also stressed the importance of adoption in India, but placed equal emphasis on ensuring adequate global supply and reducing rotavirus vaccine prices, especially to GAVI.[123] Bharat has publicly stated that it will make its vaccine available to "global public markets" at $1 per dose.[124] This price (for three doses) would represent a more than 40 percent reduction from the recently announced GSK price to GAVI. The savings to GAVI alone could easily exceed international expenditure on the development of the new vaccines. Serum has not announced a target price for its vaccine, but they told us that they expected to be able to compete with Bharat on price.

[118]MIHR/PIRPA. (2007). Rotavirus vaccine: NIH Office of Technology transfer. In Krattiger, A., Mahoney, R. T., Nelsen, L., Thomson, J. A., Bennett, A. B., Satyanarayana, K., Graff, G. D., Fernandez, C., & Kowalski, S. P. *Executive Guide to Intellectual Property Management in Health and Agricultural Innovation: A Handbook of Best Practices* (Oxford, UK: MIHR; Davis, CA: PIPRA; Rio de Janeiro: Oswaldo Cruz Foundation; and Ithaca, NY: bioDevelopments International Institute). Available at: www.ipHandbook.org.

[119]For a more complete overview of the pipeline, see Thiry, G. (2010). What does the rotavirus vaccine pipeline look like? Presentation at the 9th International Rotavirus Symposium (Johannesburg, August 2–3). Available at: www.sabin.org/files/uploads/THIRY.pdf.

[120]When immune responses that correlate with protection from infection are known, the efficacy of new vaccines can be demonstrated in smaller trials that are focused on measuring these immune responses.

[121]Interviews with Bharat and Serum.

[122]Glass, R. I., Bhan, M. K., Ray, P., Parashar, U. D., Greenberg, H., Rao, C. D., Bhandari, N., Maldonado, Y., Ward, R. L., Bernstein, D. I., & Gentsch, J. R. (2005). Development of a candidate rotavirus vaccines derived from neonatal strains in India. *J Infect Dis 192*(1): S30–35.

[123]Interview with John Boslego, July 26, 2011; interview with Georges Thiry, July 29, 2012.

[124]Bharat Biotech. (2011, June 6). Bharat Biotech announces the price of Rotavac, its potential vaccine against rotavirus diarrhea [press release]. The first version of Bharat's vaccine will have to be frozen, which may be a barrier in some immunization systems. A subsequent version will be stable when refrigerated, but it will cost somewhat more.

Case Study: Rotavirus Vaccines (continued)

It is also possible that one or more of the new vaccines may prove more effective in India than the two current vaccines. But though there are some suggestions that 116E in particular may replicate better in very young infants than GSK's vaccine,[125] most experts do not seem to be pinning their hopes on greater efficacy, as the vaccines in trials are based on similar concepts to the licensed vaccines.

It is worth noting that the goals of increasing supply, reducing price, and promoting adoption in India might also have been met by encouraging manufacture of one of the existing vaccines in India, ideally through technology transfer from GSK or Merck to an Indian supplier. This approach would be quicker and probably cheaper, even if it required substantial incentives to the multinational firm. However, GSK and Merck may not have been willing to transfer technology, and this strategy would not have accomplished the goal of building R&D capacity in India.

None of the international partners cited lower R&D costs as an argument for working with Indian researchers and manufacturers, although some costs may indeed be lower. In fact, developing these vaccines with Indian firms required overcoming several obstacles, including lack of experience with large community trials, lack of facilities for preclinical testing, and a regulatory requirement that new vaccines be tested first abroad. It is likely that these candidates could have been brought to market more quickly, and with less need for technical assistance, with a U.S. or European industrial partner. From the PATH/Gates perspective, the choice of an Indian (as well as a Chinese) partner can be considered an investment in long-term lower price and supply security. For both the Indian government and international partners, support to the rotavirus programs is also an investment in vaccine R&D capacity, which should facilitate the development of other vaccines of public health importance in India and globally.

What are the motivations of the Indian firms? According to our interviews, Bharat, Serum, and Shantha find the rotavirus vaccine market, which could reach 200 million doses in GAVI-eligible and graduating countries alone,[126] commercially attractive. Serum believes that this market can support four firms, and, indeed, even at $1 per dose, revenues from a quarter-share of the market would be very substantial compared with Serum's current revenues. Shantha suggested that the number of firms that could share the market could be even higher. Bharat said that total sales of 200–300 million doses would make the project a commercial success. On the other hand, there would almost certainly be excess supply if all the vaccines currently in development were to reach market. Serum and Bharat also benefit from the technical support they receive from PATH and other partners, particularly in the design and conduct of large community trials, whereas Shantha receives financial and technical support from Sanofi, its parent company.

It is too early to say whether the extensive investment that DBT, NIH, and PATH have made in Indian rotavirus vaccine development will pay off, as none of the candidate vaccines has yet reached market. However, all participants are optimistic, and the development of the Bharat candidate can already serve as a model of sustained collaboration in vaccine development among the India government, public-sector researchers, Indian industry, international technical partners, and international donors.

[125]Bhandari, N., et al (2006). Safety and immunogenicity of two live attenuated human rotavirus vaccine candidates, 116E and I321, in infants: Results of a randomized controlled trial. *Vaccine 24*(31–32): 5817–23.

[126]UNICEF Supply Division. (2012). Update on rotavirus vaccine. Presentation at the Industry Consultation Meeting (Copenhagen, Denmark, January 25–26).

CHAPTER 4
DRUGS

4 India has a vibrant and rapidly growing drug industry, which now competes successfully in the United States and other lucrative, high-income markets.

This section addresses the potential of this industry to contribute to the development of new medicines for neglected diseases important in India and other developing countries.

New Drug Needs for Neglected Diseases

The problem of ensuring access to existing drugs, especially antiretroviral therapies for HIV, has dominated debates over medicines for developing countries. However, there is also an urgent need for new medicines for many important diseases in low- and middle-income countries. For some diseases, including dengue and chronic Chagas, there are no effective medicines; for others, such as sleeping sickness, existing drugs have dangerous side effects or require complicated or lengthy treatment protocols that may not be feasible in some settings or that may discourage patients from completing therapies.[127] Even when good drugs are available, the threat of resistance looms, as illustrated by the recent emergence of resistance to artemisinin-based antimalarials in Southeast Asia and the well-established problem of drug-resistant tuberculosis. Resistance to common antibiotics is already a major problem in both high-income and developing countries.

In addition to new drugs, there is a great need for more incremental improvements to existing drugs, including the development of more convenient presentations, pediatric formulations, and fixed-dose combinations. Table 4.1 gives an overview of drugs available for neglected diseases.

Although this report focuses primarily on infectious diseases, the burden of noncommunicable diseases is also very high and growing rapidly in developing countries. Although the importance of these diseases in high-income countries creates strong incentives for drug development, the distinct circumstances of developing countries, including much smaller health budgets, weaker health systems, and differences in epidemiology and disease presentation, may create special needs for new and adapted drugs for these diseases.

Despite the great need, only a small fraction of global drug R&D spending is devoted to neglected diseases. According to the most recent G-FINDER survey, $654.3 million was spent in 2010 on developing new drugs for these diseases,[128] whereas pharmaceutical companies alone spent $68 billion.[129]

[127]Medecins sans Frontieres and International Union Against Tuberculosis and Lung Disease. (2011). DR-TB Drugs Under the Microscope. Rowland, K. (2012). Totally drug-resistant TB emerges in India. *Nature News*. Available at: www.nature.com/news/totally-drug-resistant-tb-emerges-in-india-1.9797. BIOVentures for Global Health Primer, available at: www.bvgh.org/Biopharmaceutical-Solutions/Global-Health-Primer.aspx.

[128]Moran, M., Guzman, J., Henderson, K., Abela-Oversteegen, L., Wu, L., Omune, B., Gouglas, D., Chapman, N., & Zmudzki, F. (2011). Neglected disease research and development: Is the global financial crisis changing R&D?" *Policy Cures*: 66-7.

[129]Reuters. (2011, June 26). Drug R&D spending fell in 2010, and heading lower." Available at: www.reuters.com/article/2011/06/26/pharmaceuticals-rd-idUSL6E7HO1BL20110626.

Table 4.1: Drugs Available for Neglected Diseases

Disease	Current Drugs Used
Buruli ulcer	Antibiotics
Chagas	Shorter, cheaper, and safer drug needed for acute disease; no drugs available for chronic disease
Cholera	Oral rehydration
Dengue	None
Dracunculiasis (Guinea worm)	None
E. coli	Oral rehydration; bacteria is resistant to many antibiotics
Fascioliasis	Drug available, but resistance is on the rise
Human African trypanosomiasis	New treatment recently developed
HIV	Antiretroviral therapy available, access variable, fixed-dose combinations needed for pediatric patients
Leishmaniasis	Drugs available, resistance on the rise
Leprosy	Antibiotics, some resistance reported
Lymphatic filariasis	Safer, more effective drugs needed
Malaria	Artemisinin-combination therapy, some resistance reported
Onchocerciasis	Some drugs available, with variable effectiveness
Pneumococcal disease	Antibiotics
Rotavirus	Rehydration
Shigellosis	Rehydration, antibiotics
Soil-transmitted helminths (hookworm, ascariasis, trichuriasis)	Drugs available
Trachoma	Antibiotics
Tuberculosis	Need for shorter treatments and cheaper and safer second-line drugs; resistance on the rise; new pediatric formulations needed
Typhoid	Rehydration; antibiotics; resistance on the rise
Yaws	Antibiotics

Source: BIO Ventures for Global Health Primer, accessed March 18, 2012. Available at: http://www.bvgh.org/Biopharmaceutical-Solutions/Global-Health-Primer.aspx

As a result, of the 1,393 new drugs approved between 1975 and 1999, only 16 were for tropical diseases and tuberculosis.[130] (These figures include only "new chemical entities," not new formulations or combinations of existing drugs.)

Outline of Drug Development

Drug development is generally built on a platform of basic research on a specific disease and, in the case of infectious diseases, on the pathogen—the virus, bacterium, or parasite that causes the disease.[131] This research usually occurs in academic or public research settings. The knowledge derived from basic research is then used to identify molecules that might be able to treat the disease. This stage in drug development, called drug discovery, now happens predominately, but not exclusively, in industry. In recent years, industry has relied heavily on a strategy of "high-throughput screening," in which thousands of molecules are synthesized to create a molecular "library" and are then evaluated for their ability to block processes believed to be essential for disease progression.[132] The promising molecules, or "hits," are subjected to additional tests, which narrow the list of candidates. These "leads" are then optimized by a process of chemical modification and further testing.[133] High rates of attrition occur in this phase, and companies often refine and adapt a particular drug candidate many times.

This description of drug discovery applies to so-called small-molecule drugs. An increasing number of new drugs are large biological molecules, which are developed using molecular genetics and biotechnological approaches. These "biologics," thus far, have been less relevant to infectious diseases; thus, we focus primarily on traditional small molecular drugs.

If all goes well, candidates that emerge from this discovery process are tested in animals. Afterward, candidates can be tested for safety and efficacy in humans in clinical trials,[134] which progress from small phase I to large phase III trials. Although small companies often engage in lead-optimization and other preclinical activities, large multinational corporations (MNCs) are generally responsible for clinical development. Once a drug enters the market, further monitoring studies are conducted to verify its safety; in addition, further studies and R&D are often needed to adapt a drug for special populations, such as children. Even once a drug is approved, R&D can continue in order to develop new formulations and delivery methods for a drug and to create combination treatments that combine multiple active ingredients into a single pill. This end-stage R&D usually requires smaller investments and is often an area of strength for generic firms.

The drug development process is long (10 years or more), expensive, and risky, and candidates can fail at any stage. The true costs of drug development have been debated. One oft-cited estimate puts the full cost per new drug as high as $800 million, though others have challenged this figure.[135] The high costs of failed drug candidates must be recovered from the profits of a successful drug, which deters companies from investing in new drug R&D for products with small returns.

[130]Trouiller, P., Olliaro, P., Toreels, E., Orbinski, J., Laing, R., & Ford, N. (2002). Drug development for neglected disease: A deficient market and public-health policy failure. *Lancet 359*(9324): 2188–94.

[131]Lowell, J. E. (2007). Closing the Global Health Innovation Gap: A Role for the Biotechnology Industry in Drug Discovery for Neglected Diseases. (*BIO*Ventures for Global Health, Washington, DC).

[132]Ibid.

[133]Ibid.

[134]Ibid.

[135]DiMasi, J. & Hansen, R.W. & Grabowski, H.G. (2003)The price of innovation: new estimates of drug development costs. *Journal of Health Econ* 22: 151-85. Collier, R. (2009). Drug development costs hard to swallow. CMAJ 180(3): 279–80. Light, D. W., & Warburton, R. (2011). Demythologizing the high costs of pharmaceutical research. *Biosocieties 6*: 34–50. PhRMA. (2007). Drug Discovery and Development: Understanding the R&D Process. (Washington, DC: PhRMA).

For neglected diseases, most new drug development is taking place in academic settings and through product development partnerships (PDPs).[136] About 173 drug candidates are in development for neglected diseases, though the majority of this activity represents R&D for HIV/AIDS, malaria and TB, and candidates in the discovery and preclinical stages of development.[137] Given the high rates of attrition in drug development, the pipeline is far from adequate.

Low-income countries need both new and cheaper drugs to better control disease, and India has established itself as an important supplier of low-cost generic drugs. Generic production is enormously important for drug access, and India will continue to play a vital role. However, although bringing a generic drug to market does require some innovation—in particular, chemical process development—this type of R&D is relatively straightforward and inexpensive. We focus in this section on India's role in the development of new drugs and its potential contribution to neglected disease.

Industry Overview

Although the leading drug producers are now all in the private sector, Indian government policies and initiatives have played an important role in creating the industry. After independence, the government of India (GOI) created two public companies, Hindustan Antibiotics and Indian Drugs and Pharmaceutical Ltd., to produce essential bulk drugs for the country. These public enterprises laid the foundation for India's pharma industry by creating demand for the services and inputs of supporting industries and for science graduates of Indian universities.[138] Moreover, some of the founders of India's largest biopharmaceutical companies today began their careers with these groups.[139] Public-sector units continue to supply basic medicines to the public sector and, in 2010–2011, had a turnover of about $65.4 million.[140]

The most significant catalyst for the drug industry, however, was the Indian Patents Act of 1970, which eliminated product patents for medicines and limited on foreign ownership in most types of Indian companies.[141] Before then, foreign MNCs controlled 80–90 percent of the Indian drug market and held nearly all of the drug patents in the country.[142] The changes after 1970 allowed Indian drug firms to exploit the domestic market for drugs patented outside of India and paved the way for the generics industry that flourishes in India today. The need to invent new processes for producing these drugs (process patents were still granted) and the focus on a high-volume, low-margin market also drove the development of expertise in process chemistry and low-cost production, which remain strengths of the industry. The freedom to overlook product patents for medicines recognized in other countries lasted until 2005, when India officially complied with the agreement on Trade Related Aspects of International Property (TRIPS), in order to meet membership requirements for the World Trade Organization. The TRIPS agreement stipulates that all member countries must enforce product (and process) patents for 20 years if granted by another member, though countries retain some flexibility in which types of claims they accept.

[136]Ponder, E., & Moree, M. (2012). The Product Developer Landscape. (BIOVentures for Global Health, Washington, DC).

[137]Ibid.

[138]Chaturvedi, K. & Chataway, J. (2006). Strategic integration of knowledge in Indian pharmaceutical firms: Creating competencies for innovation. *IJBIR 1*(1–2): 27–50. Mani, S. (2006). The Sectoral System of Innovation of Indian Pharmaceutical Industry (Centre for Development Studies Working Paper 382). Government of India. (2011). *Annual Report 2010–2011* (New Delhi: Department of Pharmaceuticals).

[139]Ibid.

[140]Government of India (GOI). (2011). *Annual Report 2010–2011* (New Delhi: Department of Pharmaceuticals). The National Planning Commission Report. (New Delhi: Government of India)

[141]Government of India. (1980). The Patents Act. Available at: www.wipo.int/wipolex/en/details.jsp?id=2393

[142]Greene, W. (2007). The Emergence of India's Pharmaceutical Industry and Implications for the U.S. Generic Drug Market. (Washington, DC: Office of Economics, International Trade Commission).

The impending change in the patent regime in 2005 led to much speculation about how the Indian drug industry would evolve. Some imagined a transformation of the leading companies into innovative, internationally competitive, R&D-based enterprises, whereas others predicted the renewed dominance of foreign companies. The implications of TRIPS implementation on the price and availability of medicines became a hot topic for international debate, as India had become an important producer of generic versions of various medicines, especially HIV drugs. India's recent issuance of its first compulsory license demonstrated that the intellectual property (IP) issues related to medicines are far from settled.[143] At the same time, ongoing economic reforms were dismantling the "license Raj" and opening the private sector to greater competition. These reforms presented drugs firms with both new opportunities—greater ease of doing business and international trade—and obstacles—competition from MNCs.

In this charged and rapidly evolving policy environment, the Indian drug industry has continued to grow, turning its attention to new markets, forging partnerships with firms abroad, and making at least initial investments in new drug development. On the whole, however, most of the large firms have retained—or returned to—a primary emphasis on generics. A growing focus on developed-world markets may prove as much of a threat to Indian firms' role as suppliers of needed medicines for infectious diseases as are acquisition by MNCs or TRIPS compliance.

Markets and Business Models

The Department of Pharmaceuticals (DPT) estimated that the turnover of the Indian pharmaceutical industry was $21.7 billion in 2009–2010.[144] The Indian pharmaceutical industry caters to both international and domestic markets and includes a mix of small producers, large generic manufacturers, and firms specializing in specific aspects of drug development and manufacturing, such as clinical trials, manufacturing active pharmaceutical ingredients, or packaging. According to the DPT, there are 10,653 pharmaceutical manufacturing units in India.[145] About 300 to 400 of these units medium- to large-size firms, and the top 50 exporting firms accounted for 75 percent of domestic sales and about 90 percent of exports in 2010.[146] The largest firms are now publicly traded (in contrast to the vaccine industry, where most firms are still privately held), and they have increased their share of both domestic and export markets.[147]

A major breakthrough for India's drug industry has been its success in winning approval for its products from the U.S. Food and Drug Administration (FDA) and regulatory authorities in other high-income countries. Of the more than 2,000 approvals granted by the FDA between 2007 and 2011 for generic versions of licensed drugs, more than 30 percent went to Indian companies.[148] Exports of Indian pharmaceuticals grew from roughly $1.9 billion in 1999 to $5.1 billion by 2005; one study found that India controls more than one-fifth of the global generics market.[149] The rate of growth for exports has consistently outpaced the

[143]Kulkarni, K., and Foy, H. (2012). Analysis: India cancer ruling opens door for cheaper drugs. *Reuters*. Accessed March 27, 2012; available at: www.reuters.com/article/2012/03/13/us-india-drugs-idUSBRE82C0IN20120313.

[144]Government of India (GOI). (2011). *Annual Report 2010–2011* (Delhi: Department of Pharmaceuticals). GOI. (2009). Annual Report 2008–2009 (Delhi: Department of Pharmaceuticals).

[145]GOI (2011).

[146]Government of India. (2011). National Planning Commission Report on Drugs and Pharmaceuticals. (Delhi: Government of India).

[147]Chaudhuri, S. (2010). The Indian pharmaceutical industry after TRIPS. In Chaudhuri, S., Park, C., and Gopakumar, K. M. eds. *Five Years into the Product Patent Regime: India's Response* (New York: United Nations Development Program).

[148]IHS Global Insight. (2012). Indian companies garner 33% of ANDA approvals in 2011. Available at: www.ihs.com/products/global-insight/industry-economic-report.aspx?id=1065932080.

[149]Greene, W. (2007). The Emergence of India's Pharmaceutical Industry and Implications for the U.S. Generic Market. (Washington, DC: Office of Economics, International Trade Commission). Perlitz, U. (2008). India's pharmaceutical industry on course for globalisation. Deutsche Bank Research.

domestic market.[150] Although Europe and the United States are the most important destinations for Indian drug exports, many Indian companies export their products throughout Asia and Africa. Russia and China are among the top five importers of Indian pharmaceuticals and medicines.[151] The increasing importance to Indian firms of high-income markets inevitably brings with it an emphasis on products for these markets, as well as for the rapidly growing Indian middle class, rather than on drugs for infectious diseases affecting mostly the poor in India and other developing countries. The implications for neglected disease R&D are discussed below.

Table 4.2 presents some basic data on 10 of the largest drug producers. As these data show, although

Table 4.2: Business Data of Leading Indian Pharmaceutical Firms

	Total 2010 Sales or Income ($US millions)	Exports* as a Percentage of Total Sales or Income	Domestic Market as a Percentage of Total Sales or Income	R&D Expenditure as a Percentage of Sales or Income	Publicly Traded?
Ranbaxy Laboratories Ltd.	$1,864.1	79.4%	20.6%	5.80%	Yes
Dr. Reddy's Laboratories Ltd.**	$1,634.2	87.0%	13.0%	6.70%	Yes
Cipla	$1,413.3	51.8%	48.2%	4.40%	Yes
Lupin World	$1,251.8	68.0%	32.0%	9.20%	Yes
Aurobindo Pharma	$976.9	60.2%	39.8%	3.90%	Yes
Wockhardt	$841.0	72.0%	28.0%	0.90%	Yes
Zydus Cadila	$649.2	40.7%	59.3%	10.10%	Yes
Glenmark**	$642.5	63.3%***	36.7%***	2.20%	Yes
Mylan India (Matrix Labs)	$620.1	82.8%	17.2%	10.30%	Yes
Sun Pharmaceutical Industries Ltd.	$13.0	70.7%	29.3%	117.70%	Yes

Source: 2010–2011 Company Annual Reports, approximate figures

* Either directly reported or estimated through foreign exchange earnings (foreign exchange earnings may include other payments than export sales).

** Based on total revenues.

*** From http://planningcommission.nic.in/aboutus/committee/wrkgrp12/wg_pharma2902.pdf

(Some companies have reported for the calendar year 2010, and some have reported on the fiscal year 2010.)

[150]Indian Pharmaceutical Alliance, original data from the database of the Center for Monitoring Indian Economy

[151]GOI. (2011). *Annual Report 2010–2011*. (New Delhi: Department of Pharmaceuticals).

the largest firms are substantial enterprises, they are still much smaller than the big multinational pharmaceutical companies. For example, Pfizer and Johnson & Johnson each had revenues of more than $50 billion in 2010, and all of the top 10 international firms brought in more than $20 billion.

The domestic pharmaceutical market, almost 90 percent of which is for branded generics (that is, generics marketed under the producer's own name),[152] is growing rapidly. Indian companies meet nearly all of the country's demand for bulk drugs and formulations.[153] In 2009, the domestic pharmaceutical market reached $12.6 billion, and McKinsey projected that the market will reach at least $35 billion by 2020.[154] Public-sector spending on drugs has grown, driven by both state- and central-level expenditure.[155] In 2010–2011, total central and state spending on drugs reached $1.1 billion, or about 13 percent of the government's health expenditure and 43 rupees per capita (less than $1).[156]

Price controls have been an important feature of the Indian market. Although the number of drugs subject to these controls has been steadily reduced in recent years—as of 2005, about 10 percent of the domestic drug market was under price control[157]—the government is considering expanding the list in response to high prices for new cancer drugs.[158]

Just as Indian firms now participate in the U.S. and European markets, foreign multinationals are eager to establish a position in the growing India market, as well as to capitalize on India's strengths in low-cost production. One strategy has been to acquire India-based generic companies to complement MNCs' own R&D-driven businesses. Two of the most well-known acquisitions are Daiichi Sankyo's purchase of Ranbaxy Laboratories in 2008 and Abbott Laboratories' 2010 takeover of Nicholas Piramal's formulations business. Other acquisitions include Mylan's buyout of Matrix Laboratories and Fresenius Kabi's acquisition of Dabur.[159] These acquisitions have raised some alarm, both in India and among access-to-medicine advocates abroad, and there has been some discussion of reimposing limits on foreign ownership. India's pharmaceutical industry has expressed some concern that the dominance of MNCs in India will weaken the growth of domestic companies.[160] It is too early to tell how these acquisitions will affect the operations of the original companies, but it is worth noting that Ranbaxy has already ceded its new drug development unit to Daiichi Sankyo.

Similarly, Indian companies have acquired businesses abroad to expand their marketing and distribution networks and to access new technology.[161] In 2005 alone, Indian pharmaceutical companies spent $1.6

[152]Greene, W. (2007). *The Emergence of India's Pharmaceutical Industry and Implications for the U.S. Generic Market*. (Washington, DC: Office of Economics, International Trade Commission).

[153]Ibid.

[154]Bhadoria, V., Bhajanka, A., Chakraborty, K., & Mitra, P. (2010). *India Pharma 2020: Propelling Access and Acceptance, and Realizing True Potential.* McKinsey & Company report on Pharmaceutical and Medical Products Practice.

[155]GOI. (2011). High-level expert group report on universal health coverage for India. Instituted by the Planning Commission of India. (Delhi: Public Health Foundation).

[156]Ibid.

[157]GOI. (2005). "Report of the Task Force to Explore Options Other Than Price Control for Achieving the Objective of Making Available Life-Saving Drugs at Reasonable Prices." Submitted to the National Planning Commission of India.

[158]Singh, K. (2011). Government likely to bring cancer drugs under price control. *Economic Times*. Available at: http://articles.economictimes.indiatimes.com/2011-03-19/news/29146276_1_price-control-cancer-drugs-cancer-medicines.

[159]Chaudhuri, S. (2011). *Multinationals and monopolies pharmaceutical industry in India after TRIPS* (Indian Institute of Management Working Paper, Calcutta). Golikeri, P. (2010). Pharma mergers & acquisition wave has roots in product-patent regime. DNA. Available at: www.dnaindia.com/money/report_pharma-mergers-and-acquisition-wave-has-roots-in-product-patent-regime_1387310.

[160]Indian Pharmaceutical Alliance. (2011). "Note for Working-Group on Drugs & Pharmaceutical Industry."

[161]Tempest, B. (2011). The Structural Changes in the Global Pharmaceutical Marketplace and Their Possible Implications for Intellectual Property (International Centre for Trade and Sustainable Development Policy Brief 10). Available at www.usitc.gov/publications/332/working_papers/EC200705A.pdf.

billion on foreign buyouts, mostly in Europe.[162] These deals, as well as cross-penetration of markets, are aspects of the growing integration of India—and the Indian drug industry—into a global pharmaceutical market, with important implications for R&D priorities.

Research and Development

With the approach of TRIPS compliance in 2005, many firms increased their R&D spending, and there was excitement about the firms' potential to develop new drugs. From 2007 to 2008, the average R&D expenditure of Indian companies performing new chemical entity (NCE) R&D was about 8 percent of sales[163] (this compares with 10–20 percent for MNCs[164]). As Figure 4.1 shows, however, R&D spending for drugs was highest immediately after TRIPS implementation and has declined slightly since.[165] Indeed, several of the biggest firms have largely withdrawn from expensive and risky early-stage drug development and refocused their efforts on incremental R&D—for example, on new formulations and delivery systems in support of their generics businesses. R&D spending is still considerably higher than it was in the past, but its composition has shifted and includes a large focus on R&D for generics.[166]

According to several accounts and interviews with industry executives, this waning enthusiasm for new drug development resulted from a growing realization, on the part of firms and their investors, of the high risk of failure and the long timeline of drug R&D. Investors who supported the companies' generic activities expected faster turnaround on R&D projects and withdrew support from riskier undertakings.[167] Moreover, these investments were hard to justify when lucrative, relatively low-risk generic markets beckoned. In an attempt to reduce their exposure to R&D risk, some companies spun off their R&D units into subsidiary companies, many of which now rely on opportunities for contract research.

No Indian company has yet developed a drug from the discovery stages through phase III trials and market introduction, although the first "Indian NCE" is likely to be approved this year. A few companies, such as Dr. Reddy's Laboratories, Glenmark, Wockhardt, and Zydus Cadila, are still trying to engage in the full spectrum of R&D. Some other companies are focusing on particular areas of R&D and building partnerships with MNCs. Some companies out-license compounds for late-stage development, while others carry out defined stages of discovery or clinical development for MNCs on a contractual basis. Glenmark, for example, earned about 5.6 percent of its 2010–2011 revenues from out-licensing its molecules.[168] Both of these strategies allow Indian firms to participate in new drug development without bearing the full cost or risk. Indeed, the business models of many Indian drug firms are mixed and include a combination of branded generics, contract research or manufacturing, and new R&D. Some others are moving into biosimilars.

As firms experiment with new R&D business models and partnerships, the tendency toward specialization in specific types of R&D is likely to grow.[169] The rise of contract research organizations (CROs) is

[162]Krishnan, R. (2006). It's Europe for Ranbaxy. *Financial Express*. Available at: www.financialexpress.com/news/its-europe-for-ranbaxy/156086/2.

[163]Chaudhuri, S. (2010). The Indian pharmaceutical industry after TRIPS. In Chaudhuri, S., Park, C., and Gopakumar, K. M. eds. *Five Years into the Product Patent Regime: India's Response* (New York: United Nations Development Program).

[164]The Pharmaceutical Research and Manufacturers of America, a trade association, reported that its members spent $49.5 billion on R&D in 2011, corresponding to 16.7 percent of sales (PhRMA 2012 profile, available at: www.phrma.org/research/publications/profiles-reports).

[165]Chaudhuri (2010).

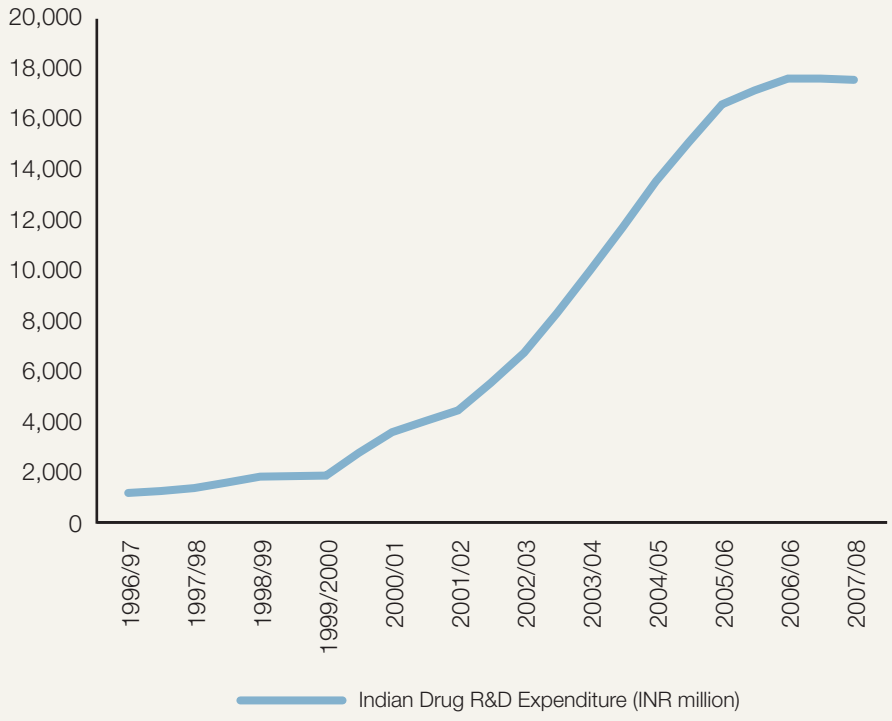
[166]Interviews and company websites

[167]Chaudhuri (2010). Sen, F. (2009). Discovery and Drug Development Business Opportunities in India. (New Delhi: Observer Research Foundation and Federation of Indian Chambers of Commerce and Industry). Interviews.

[168]Glenmark (2011). 2010–2011 Annual Report.

[169]Bruche, G. (Forthcoming). Emerging Indian pharma multinationals: Latecomer strategies in a globalised high tech industry. *European Journal of International Management*.

Figure 4.1 Indian Drug R&D Expenditure



Source: Chaudhuri, S. (2010). The Indian pharmaceutical industry after TRIPS. In Chaudhuri, S., Park, C., and Gopakumar, K. M. eds. Five Years into the Product Patent Regime: India's Response (New York: United Nations Development Program).

an important manifestation of this trend. Currently, the biggest area of CRO activity is in helping MNCs manage clinical trials, which are low-risk activities for the Indian partner. CROs have relationships with trial sites where they can quickly enroll patients in studies, and they have the necessary familiarity with the regulatory system to guide MNCs through the review process. Laws requiring that late-stage trials must be conducted in India in order for any foreign technology to enter the domestic market have contributed to the high demand for CRO services. MNCs also conduct trials in India to support licensure in other markets because of the large treatment-naive patient populations and substantial cost advantages. One analysis found that per-patient trial costs in India were half of that in the United States.[170] These cost benefits are significant for nonprofit and for-profit firms alike. A consortium of PDPs has added the Indian CRO GVK Biosciences to its list of preferred partners to manage clinical research for neglected disease.[171]

At least 100 CROs are operating in India, and the largest—the Indian arm of the multinational firm Quintiles—had revenues of slightly less than $100 million between 2010 and 2011.[172] The bioservices industry, which includes contract research across the life sciences, expanded by nearly 30 percent

[170]Boston Consulting Group. (2011). Life Sciences R&D: Changing the Innovation Equation in India. Commissioned by USA-India Chamber of Commerce.

[171]MacDonald, G. (2011). GVK to work with Gates-funded neglected disease group. Accessed June 14, 2012; available at: www.outsourcing-pharma.com/Clinical-Development/GVK-to-work-with-Gates-Foundation-funded-neglected-disease-group.

[172]Saberwal, G. (2007). Bio-business in brief: The challenges of clinical trials. *Current Science 93*(10): 1367–75. Biospectrum (2011).

between 2008 and 2009.[173] Other CROs, such as Advinus, offer services in lead optimization and other aspects of drug discovery and development. In fact, contract research may be an important avenue for Indian industry to strengthen its drug development capacities. Interviews with pharmaceutical executives suggest that cost advantages are a significant driver in MNCs' decisions to partner with Indian firms.[174] Cost savings for contract research may currently be as high as 60 percent but will decline over time; one estimate suggests that the advantage will persist, reaching a 20 percent level in 2025.[175] However, a recent review of biotech and pharmaceutical research out-sourced to India found that presently, the level of innovation involved for the Indian partner is typically low.[176]

The GOI encourages the specialization of firms and collaborations among them, because it views this as one way to allow the drug industry to move forward without waiting for the development of fully integrated companies.[177] However, the trend can perhaps be seen instead as moving toward a specialized role for Indian industry in an increasingly globalized system of drug development. Although in such a system even the big multinationals would conduct only certain aspects of R&D in house, they would retain control over R&D priorities. Indeed, since the R&D priorities of the MNCs are unlikely to include neglected diseases, the growth of contract R&D in India does not bode well for involvement of Indian industry in neglected disease projects. But given that Indian drug firms are focused on export and fast-growing segments of the Indian market, their own R&D priorities may not be all that different from those of the MNCs (see the next sub section).

Although CROs offer a broad range of R&D services and some of the large drug producers are still pursuing an integrated model of new drug development, India's greatest strength in drug R&D is probably still in synthesis and process development. Most executives and experts interviewed for this report agreed that capacities in drug discovery are still relatively limited. In particular, except for a modest facility maintained by the Central Drug Research Institute, there are almost no small-molecule libraries in either the public or the private sector. In addition, few if any companies are doing high-throughput screening.[178] And although many firms may be able to carry out defined tasks well, the capacity for highly innovative work and for managing the overall process is apparently still limited.

Research and Development for Neglected Diseases

Although India's importance in supplying generic drugs to global health markets cannot be overstated, Indian firms are playing a limited role in new drug development for neglected diseases. Ranbaxy is moving forward with an antimalarial compound inherited from Medicines for Malaria Ventures (MMV), and Lupin was developing a new TB drug with support from the Indian government (the fate of this candidate is unclear). Wockhardt is actively developing its anti-infectives portfolio, which may pertain to diseases important for both low- and high-income populations. Drawing from work conducted in the public sector, Lifecare Innovations, with funding from the Small Business Innovation Research Initiative (SBIRI), introduced India's first liposomal treatment for visceral leishmaniasis, known as kala-azar. In addition, Advinus is in the early stages of developing treatments for this disease.

[173]Biospectrum (2011).

[174]Boston Consulting Group. (2011). Life Sciences R&D: Changing the Innovation Equation in India. Commissioned by USA-India Chamber of Commerce.

[175]Ibid.

[176]Soby, S., Kandaswamy, M., & Saberwal, G. (2012). Work outsourced to Indian biotech and pharma companies is not yet significantly innovative. *Current Science 102*(3): 401–04.

[177]Sen, F. (2009). Discovery and Drug Development Business Opportunities in India. (New Delhi: Observer Research Foundation and Federation of Indian Chambers of Commerce and Industry).

[178]Interviews

Box 4.1: Drug Development Initiatives in the Public Sector

Open Source Drug Discovery (OSDD). OSDD is an initiative within the Council of Scientific and Industrial Research (CSIR) that promotes collaborative approaches to developing TB drugs. OSDD's online platform connects thousands of users to collaborate on large projects, such as annotating the TB genome. OSDD uses a transparent peer review process to review and fund new project proposals. All ideas are attributed to individual users. However, the resulting intellectual property remains with CSIR and is freely available for licensing. OSDD is in the process of creating an open-access repository that will make molecules freely available for further screening, and it is currently validating 18 drug targets. Until now, the program has focused on early-stage research; however, as its candidates progress, it is moving toward late-stage development activities. The TB Alliance and OSDD have announced a partnership for advancing clinical trials in India, though the activities are not yet under way (OSDD-TB Alliance joint press release, March 2012). The program has also taken initial steps to include research for antimalarials in its portfolio (interviews). This new research program will be coordinated by the Central Drug Research Institute. The expansion of this program suggests a growing government commitment to collaborative approaches to R&D.

Central Drug Research Institute (CDRI). CDRI, a part of CSIR's network of institutes and laboratories, is intended to have full drug development capacity. Although the institute focuses on a mix of disease areas, it pursues many projects related to neglected disease. CDRI maintains one of two primate research facilities in the country and a high-throughput screening facility that can be used by other groups and industry (Sen 2009).

Table 4.3 summarizes information on R&D activities at leading firms, derived from their websites. As this table illustrates, R&D portfolios of Indian pharmaceutical firms include products for both communicable and noncommunicable diseases, but few for TB, malaria, or neglected tropical diseases.

A survey of 49 of the 75 largest drug firms in India found that at least 65 percent of the participants conducted some R&D for local diseases, but this may not necessarily signify R&D for new drug development or for neglected infectious diseases.[179] Many of the NCEs that are currently in phase I or II clinical trials address diabetes, cancer, and pain.[180] The disease focus of companies pursuing contract research and licensing partnerships with MNCs presumably reflects the research priorities of Western companies.

The most significant involvement of Indian firms in neglected disease continues to be in low-cost generics. Indian generic companies supply 80 percent of the donor-funded generic antiretroviral (ARV) market by volume. In addition, of the 11 WHO-prequalified antimalarials, seven are supplied by Indian firms.[181] They also play an important role in TB and other infectious diseases products, such as broad-spectrum antibiotics. The relatively low cost of developing a generic drug—as little as $1 or $2 million—means that relatively small markets (perhaps $5 million) can be attractive to firms. However, the much greater cost and risk of developing a new drug means that markets must be much larger to justify the investment. One Indian executive explained that for a new drug, a $1 billion global market is desirable, and a $500 million market is still viable, but markets under $200 million would mean losses for the company. The Indian Pharmaceutical Alliance estimates that it would take an Indian firm roughly $200 million and 10 years to bring an NCE to market.[182]

Interviewees agreed that investment in neglected disease R&D is not in general more attractive to Indian firms than to the multinationals. Public funding agencies or private donors would have to derisk R&D through push or pull financing in order to engage large Indian drug firms.

[179]Sampath, P. G. (2008). India's Pharmaceutical Sector in 2008 Emerging Strategies and Global and Local Implications for Access to Medicines. (London: Department for International Development).

[180]Chaudhuri, S. (2010). The Indian pharmaceutical industry after TRIPS. In Chaudhuri, S., Park, C., and Gopakumar, K. M. eds. *Five Years into the Product Patent Regime: India's Response* (New York: United Nations Development Program).

[181]Waning, B., Diedrichson, E., & Moon, S. (2010). The lifeline to treatment: The role of Indian generic manufacturers in supplying antiretrovirals to development countries. *J Int AIDS Soc 13*(35).

[182]Indian Pharmaceutical Alliance. (2011). Note for Working Group on Drugs and Pharmaceutical Industry.

Table 4.3: Overview of R&D Programs of Indian Drug Firms

Firm	R&D for New Technologies
Aurobindo Pharma	Aurobindo's R&D program concentrates on developing noninfringing chemical processes and developing new drug delivery systems and new formulations. The company has a broad disease focus and currently sells medicines for the following infectious diseases: hepatitis C, HIV/AIDS, and broad-spectrum antibiotics.
Cipla	Cipla's R&D largely focuses on new process development and delivery systems. The company's annual report notes intentions to move into new drug development.
Dr. Reddy's Laboratories	In addition to research in generics and biosimilars, Dr. Reddy's Labs is conducting R&D for new chemical entities in three main areas: antibiotics against *Staphylococcus aureus, Pseudomonas aeruginosa*, and *Acinetobacter baumannii*; metabolic disorders; and pain/inflammation.
Glenmark	Glenmark is conducting R&D for both new chemical and biological entities. The company's disease focus includes adult diarrhea, pain, inflammation, oncology and autoimmune disorders. Glenmark maintains one R&D facility in India and two in Europe.
Mylan India	Mylan India (formerly Matrix Labs) primarily conducts generics R&D for active pharmaceutical ingredients and formulations. Their generics portfolio is quite large and includes antibiotics, antiretrovirals, and antimalarials.
Piramal Healthcare Ltd.	Piramal Healthcare Ltd., the new chemical entity research subsidiary of the broader Piramal Healthcare Group, is developing candidates in the following areas: oncology, inflammation, diabetes/metabolic disorders, and infectious diseases (such as herpes simplex virus and methicillin-resistant *Staphylococcus aureus*).
Lupin	In addition to research in generics, Lupin maintains R&D programs in new drugs and biotechnology, For new drug development, the company's therapeutic targets include diabetes, pain, autoimmune disease, cancer, and infectious disease.
Ranbaxy	Since Ranbaxy's new drug discovery program was transferred to Daiichi Sankyo, its Indian R&D operations focus on new drug delivery systems and formulations. Ranbaxy is continuing to manage the clinical development of its antimalaria candidate in India.
Sun Pharma	Sun Pharma carries out R&D for new generics formulations.
Wockhardt	Wockhardt's new drug discovery program concentrates on broad-spectrum antibiotics. Its biosimilars R&D targets chronic disease.
Zydus Cadila	Zydus Cadila's discovery program largely focuses on chronic diseases such as diabetes, osteoporosis, and renal failure. The company is participating in a collaborative rabies program with the WHO to develop a cocktail treatment using monoclonal antibodies.

Sources: Company websites, accessed March 3, 2012.

Research and Development Obstacles

In addition to remaining limitations in R&D capacity, Indian drug firms cited some of the same obstacles to R&D discussed in the overview and the sections on vaccines, including issues with human resources, public procurement, and regulatory environment. We mention here some issues specific to the drug industry.

Financing

Access to financing was not raised as a significant barrier in our interviews with firms. Unlike vaccine and diagnostic companies, which tend to be privately held, the majority of established Indian drug firms are publicly traded and are experienced in raising funds through capital markets. However, as noted earlier, Indian investors are less comfortable investing heavily in risky R&D enterprises, which may pose a challenge should established firms decide to make a large investment in new drug R&D.

Financing may also limit opportunities for new innovation-driven companies to enter the market. Nearly all of the major drug firms were founded in the 1980s or earlier.[183] Equity financing is also limited for projects with small returns, such as drugs for neglected diseases, in India as elsewhere, especially as long as unexploited high-return opportunities remain. The Department of Pharmaceuticals considered setting up a multibillion-dollar venture capital fund for pharmaceuticals, but this has yet to be implemented.[184]

The large drug firms reported less use of government financing for R&D compared with vaccine and diagnostic companies, which may reflect a greater reliance on internal funding for supporting new projects and a reluctance to navigate the public funding bureaucracy.

Intellectual Property

The 2005 changes in the Indian IP regime have fundamentally altered the business models of Indian firms. However, firms reported that they have accommodated these changes into their operations. Some are investing in new drug development while developing generics for off-patent drugs, and others, like Cipla, have aggressively challenged patents held by MNCs in order to open markets to new generic products.[185] The implementation of TRIPS certainly encouraged more firms to consider investments in new drug development, though it is difficult to say whether firms would have invested in earlier-stage R&D in the absence of this policy change. For many firms, investing in earlier-stage R&D, rather than generics, may have been a natural next step in their growth.

In interviews for this report, executives said they did not see IP as an important barrier to *new* drug (as opposed to *generic*) R&D. Firms have invested in capacity to survey patent landscapes and determine freedom to operate, though their capacity to manage IP presumably remains a fraction of that of the MNC giants. For some drug firms, patents have become tools to protect their market shares as they develop new formulations and other incremental innovations and expand into new markets. On the whole, however, the level of patenting for pharmaceutical technology is highest in the public sector.[186]

Although Indian firms may not perceive patents as an important obstacle to their current business models, the extensive patenting of compounds that are not currently in use to protect the market exclusivity of a drug (but that were developed over the course of a company's research) may block research opportunities that Indian firms would otherwise be well positioned to pursue. For example, these patents may prevent Indian companies from exploring

[183]Company websites and annual reports.

[184]Seal, V. (2010). Government mulls rupee 10,000 crore VC fund for pharma. *DNA*. Available at: www.dnaindia.com/money/report_govt-mulls-rs10000-crore-vc-fund-for-pharma_1408985.

[185]Chaudhuri, S. (2010). The Indian pharmaceutical industry after TRIPS. In Chaudhuri, S., Park, C., and Gopakumar, K. M. eds. *Five Years into the Product Patent Regime: India's Response* (New York: United Nations Development Program).

[186]Government of India. (2011). Report of the Drugs and Pharmaceuticals Working Group. (Delhi: National Planning Commission). Available at: http://planningcommission.nic.in/aboutus/committee/wrkgrp12/wg_pharma2902.pdf.

whether compounds that were originally developed for other purposes (but that are currently in disuse) could be used to treat neglected diseases. Firms have adjusted to the current IP regime in India, but overall, the needs of neglected disease R&D in particular may be better met by another IP model.

Global Industry Trends

The evolution of drug R&D in India is occurring against a background of declining productivity of small-molecule drug development across the industry as a whole, even in the most successful multinational companies[187] (this theme came up in almost all of our conversations with Indian executives). The number of new molecules winning regulatory approval has declined, despite increasing R&D expenditure. High costs and declining returns have led many experts to question the reigning model of high-throughput screening, in which promising molecules are identified by screening very large numbers of compounds against in simplified in vitro assays.[188] There is a strong desire to find new approaches that would allow developers to better focus their efforts and reduce attrition in subsequent states of development.

Indian firms have not had the resources or the technology to pursue the kind of brute force screening employed by the big firms. Making a virtue of necessity, some firms suggested that they are pursuing a more "rational" course of drug discovery that reduces uncertainty. However, it is not clear what this means in practice or what comparative advantage Indian firms bring to such an alternative model. As new approaches are developed and validated, Indian companies may be well positioned to adapt their R&D models, because they have much less invested in the current system. The growing use of information technology in health R&D may also play to India's strengths. At the same time, there is little doubt that the current climate of gloom in drug discovery has contributed to the reluctance of most Indian firms to make big investments in this area.

Public-Sector Champions

The Indian drug industry lacks high-level champions in the government that work to bring various GOI departments and agencies and international partners together to advance neglected disease drug R&D in India. There is also an absence of targeted programs and policies to overcome the barriers for new drug development in India, especially for neglected disease. Although drug companies can benefit from government programs that support R&D across sectors, such as loans from the New Millennium Indian Technology Leadership Initiative (NMITLI) or the Technology Development Board, few programs focus exclusively on new small-molecule drug development. The creation of the DPT was a step toward meeting this need, but the GOI's own research has found that the department does not have the human resource capacity to meet its full mandate and that its R&D unit is weak.[189] Although the DPT has many commendable goals, from developing pharmaceutical infrastructure to incentivizing the development of drugs for diseases endemic in India, its work in supporting new small-molecule drug development is progressing slowly.[190]

Conclusions

The Indian drug industry is making a significant contribution to global health through the provision of low-cost generic ARVs, antimalarials, antibiotics, and other important medicines to aggregated markets like the Global Fund and the Global Drug Facility, as

[187]O'Hagan, P., & Farkas, C. (2009). Bringing pharma R&D back to health [Bain & Co. brief].

[188]Scannell, J. W., Blanckley, A., Boldon, H., & Warrington, B. Diagnosing the Decline in Pharmaceutical R&D Efficiency. *Nature Reviews Drug Discovery 11*(3): 191-200. Available at: www.nature.com/nrd/journal/v11/n3/full/nrd3681.html.

[189]Government of India. (2011). *Report of the Drugs and Pharmaceuticals Working Group*. (Delhi: National Planning Commission). Available at: http://planningcommission.nic.in/aboutus/committee/wrkgrp12/wg_pharma2902.pdf.

[190]Ibid.

well as directly to developing countries. Companies are continuing to expand not only their marketing and distribution partnerships abroad but also their research collaborations. They will continue to play a crucial role in supplying affordable treatments for both communicable and noncommunicable diseases.

The prospects for Indian drug firms to play a larger role in neglected disease R&D are less promising, however. After an initial period of substantial investment in new drug development, many of the larger Indian firms have refocused their R&D expenditure on incremental innovation related to their core generics business. Moreover, their growing focus on exports to high-income countries means that even this incremental R&D is mostly directed toward noncommunicable diseases and Western markets, as is the growth of contract R&D for multinational companies. Very few products for neglected diseases are included in the portfolios of Indian firms, and executives interviewed for this project did not see such products as being commercially viable. Since drug firms tend to be publicly traded and are already integrated into global markets, management has less freedom to pursue projects with small returns out of the public health interest.

The capacity of Indian firms to develop new drugs also remains fairly limited, though this capacity is growing, as manifested in the expansion of contract research and licensing partnerships. This development may offer opportunities to engage Indian firms in particular aspects of neglected disease R&D on a contract basis, even if the big firms are not interested in markets for these products as commercial opportunities.

One area in which Indian firms could continue to play an important role is in the development of new combinations and formulations of existing drugs, including (but not limited to) antiretrovirals. It also makes sense for international neglected disease R&D initiatives to take advantage of India's cost advantages in certain aspects of drug development. In fact, the Indian CRO GVK Biosciences has been chosen as one of a small number of preferred providers to a consortium of international PDPs.[191]

In addition, the large volume of sales generated by the generics business leaves many Indian companies cash-rich. As such, some firms have created corporate social responsibility programs or foundations to support local needs.[192] Although these programs tend to focus on drug donations or support of local social initiatives, they could be a potential source of funding for neglected disease R&D.

[191]GVK Biosciences. (2011, May 16). GVK Biosciences is the preferred provider to global health Product Development Partners Consortium to focus on drugs and vaccines for neglected infectious diseases [press release].

[192]Company interviews and websites.

CHAPTER 5
DIAGNOSTICS

5

This chapter focuses on in vitro diagnostic tests on patient samples (blood, urine, sputum, and so forth), which are most relevant for infectious diseases.

Diagnostic technologies also include sophisticated scanners and in vivo devices, but these are not discussed here.

New Diagnostic Needs in Developing Countries

Diagnostic tests can play several roles in combating disease. In addition to initial diagnosis to refer patients for treatment, tests can be important in detecting drug susceptibility, in monitoring treatment side effects and response, in blood screening, and, at the population level, in measuring disease burden. Diagnostics for neglected diseases have received less attention—and far less R&D funding—than drugs or vaccines. In 2008, only 4 percent of global investment in new products for neglected diseases went to diagnostics; even in the case of tuberculosis, for which improved diagnostics are sorely needed, diagnostics received only 8 percent of research funding between 2005 and 2009.[193]

New diagnostic technologies could make a big—and, in some cases, transformative—difference for many diseases.[194] In certain cases, no good test exists at all. For example, there is no good way to diagnose TB in children or to tell whether a Chagas patient has been cured by drug treatment. In many other cases, existing tests are too expensive, require invasive procedures, or need more infrastructure or training than is widely available in many high-burden settings. In particular, the control of many infectious diseases would benefit greatly from simple, cheap, point-of-care tests, similar to the rapid tests now available for malaria and HIV, which can be used by relatively untrained healthcare workers in community settings. The particular test or tests that would have the greatest impact depends on the disease, the control strategy, and the characteristics of the health system. Thus, point-of-care tests may not always be the highest priority.

The need for improved diagnostics for developing countries is being recognized just as a number of new technologies in molecular biology, materials, and microfluidics are becoming available that have the potential to lead to cheap, powerful new tests, including rapid, point-of-care tests.[195]

The case of TB illustrates the importance of diagnostics, as well as the complexities involved in defining R&D priorities. Microscopy—examination by trained technicians

[193]Mehta, P., & Cook, D., with Health Advances LLC. (2010). The Diagnostics Innovation Map. *BIOVentures for Global Health* (citing G-Finder 2009). For TB: Salazar, J. E. (2010). Report on tuberculosis research funding trends, 2005–2009. In Harrington M., et al., eds. *Tuberculosis Research & Development* (New York: Treatment Action Group).

[194]See Mabey, D., Peeling, R. W., Ustianowski, A., & Perkins, M. D. (2004). Diagnostics for the developing world. *Nat Rev Microbiol 2*(3): 231–40. Urdea, M., et al. (2006). Requirements for high impact diagnostics in the developing world. *Nature 444*(1):S73–79. FIND website http://www.finddiagnostics.org/

[195]Mehta, P., & Cook, D., with Health Advances LLC. (2010). The Diagnostics Innovation Map. (*BIOVentures for Global Health*, Washington, DC). Chapter 4. Kolberg, J., Penny, L., Todd, J., & Urdea, M. (2009). *An Assessment of the Technological Issues and Options for Point-of-Care Diagnostic Tests in Resource-Limited Settings* (Haltere Associates white paper).

of stained sputum samples—remains the mainstay of most TB programs in low- and middle-income countries, but it has many shortcomings. New technologies that could address some of these shortcomings could have an important impact on the epidemic, but there has not been consensus on which improved characteristics are the most important. TB diagnostics are considered in detail at the end of this section.

Other examples of diagnostic needs for neglected diseases are cheaper CD4 tests to monitor HIV treatment, tests for leishmaniasis and sleeping sickness that do not require invasive procedures, and tests that could simultaneously assay for several common causes of childhood fevers.

In vitro diagnostic tests typically involve a detection platform of some kind, which can be a large and expensive machine or a cheap disposable kit, and reagents for the detection of a biomarker, which could be a protein antigen, an antibody, a volatile organic compound, or a nucleic acid (DNA or RNA). Diagnostics platforms, in the sense of both technologies and actual machines embodying these technologies, can often be used for a variety of tests, with important implications for several aspects of product development. In particular, developing a new test can be relatively cheap and easy if validated biomarkers and an appropriate detection platform are already available, but very challenging if one or the other is not at hand, as in the case of point-of-care TB diagnostics. Moreover, this feature of many platforms opens the possibility of multiplex assays that test for several diseases at once. On the other hand, inventors of a diagnostic platform may be reluctant to grant access to their technology for a neglected disease application for fear that it could also be used to produce tests for lucrative high-income markets.

In general, biomarker discovery happens in the public sector, at universities or public-sector research institutes, whereas the development and commercialization of diagnostic platforms and specific tests usually involve industry.

The current generation of cheap, rapid diagnostic tests for infectious diseases relies on the detection of pathogen antigens or host antibodies, using simple lateral flow or dipstick devices, such as those used in malaria rapid tests or home pregnancy tests. The main challenge for neglected disease diagnosis is either to find biomarkers that can work with these established low-cost platforms or to develop cheaper and more accessible technologies for detecting other classes of biomarkers, including nucleic acids.

Industry Overview and Markets

The diagnostics industry is challenging to characterize, as many overviews include suppliers of diagnostic services (laboratories) as well as suppliers of equipment and reagents, and the industry is very diverse. Not all descriptions distinguish between in vitro diagnostics and devices. India is said to have more than 10,000 diagnostic laboratories and, according to one report, at least 150 companies making tests.[196] However, only a small fraction of the laboratory sector is described as "organized," and the number of companies with a meaningful capacity to develop new tests is much smaller.

Estimates of the size of the Indian in vitro diagnostics market vary widely, but the best guess seems to be about $500 million.[197] This is similar to the vaccine market and but much smaller than the $10–15 billion Indian market for drugs. For comparison, the global market for in vitro diagnostics is estimated at about $44 billion.[198] Like Indian drug and vaccine markets, the

[196]FinPro. (2008). *Diagnostic Center Feasibility Study—India*.

[197]The most recent BioSpectrum-ABLE company survey and a recent market research report reached similar conclusions. BioSpectrum. (2011). *BioSpectrum-ABLE biotech industry survey 2011*. (India). McEvoy & Farmer market report, cited in McEvoy, C. (2012). China and India: Comparing two fast-growing IVD markets. *IVD Technology 18*(2). Available at: www.ivdtechnology.com/article/china-and-india-comparing-two-fast-growing-ivd-markets.

[198]Marketsandmarkets.com. (2012): In-vitro diagnostics trends and global forecasts (2011–2016). Available at http://www.marketsandmarkets.com/Market-Reports/in-vitro-diagnostics-ivd-market-547.html. Renub Research. (2010). Global in vitro diagnostics market trends and future forecast (2009–2014). Available at http://www.bharatbook.com/market-research-reports/healthcare-market-research-report/global-in-vitro-diagnostics-ivdmarket-trends-and-future-forecast-2009-2014.html.

market for diagnostics is said to be growing rapidly, by an average of more than 10 percent over the past 15 years and by 22 percent in the past year alone.[199] The domestic market for diagnostic tests is primarily hospitals, both public and private, and laboratories. Hospitals are said to account for 65 percent of sales.[200]

Although it is difficult to determine what share of this market is controlled by Indian test manufacturers, foreign multinationals seem to have a larger share than is the case for drugs and vaccines, especially for more sophisticated products such as molecular (nucleic acid) tests. According to one source, "Almost 80–90% of testing equipment and reagents are procured from international companies," but the basis for this claim is not clear.[201] International firms dominate the market for devices, which are less relevant for infectious diseases.

Among the leading Indian firms are the Tulip Group (which includes Orchid and several other firms), J Mitra, TransAsia, RFCL, and Span Diagnostics. These companies are substantially smaller than the leading drug and vaccine companies. For example, TransAsia and Tulip, which made BioSpectrum's list of the top 20 Indian biotech companies, had revenues of $70 and $37 million, respectively, in 2010–2011.[202] These firms supply a broad range of biochemical and serological tests, including rapid tests for HIV, malaria, hepatitis B and C, and dengue fever.[203] Some also sell serological tests for TB, which have recently been discouraged by WHO.[204] Indian firms do not seem to have moved strongly into molecular diagnostics, though this is said to be a big area of investment.[205] As with drugs and vaccines, Indian firms have focused primarily on supplying low-cost versions of tests developed elsewhere, rather than developing entirely new technologies.

There is no formal generic regulatory pathway for diagnostics, however, so these products are best thought of as follow-on versions rather than as precise reproductions of first-to-market products.

In addition to the larger producers of traditional types of tests, there are also a small number of new R&D-focused biotech companies focusing on diagnostics. These companies include XCyton Diagnostics, Bigtec Labs, Rea Matrix, and Achira Labs. These firms have expertise in molecular biology, microfluidics, and electronics, and may be capable of developing new point-of-care platforms as well as new tests for established platforms (see the TB diagnostics case study). However, this segment of the industry is almost certainly still very small, with no more than a handful of firms, and with limited capacity for manufacturing scale-up.

The larger Indian diagnostic firms have become important suppliers of some diagnostic tests to international disease control initiatives. In particular, Orchid's malaria rapid test accounted for more than half of sales between 2004 and 2009, though this share seems to have fallen precipitously since.[206] Although many Indian firms produce HIV rapid tests, they have not gained a significant share of the Global Fund market.

Many public-sector institutes are involved in diagnostic development. For example, the International Center for Genetic Engineering and Biotechnology (ICGEB) has developed tests for dengue and hepatitis C and is working on new technologies for TB diagnosis. Likewise, All India Institute of Medical Sciences (AIIMS) has developed tests for extrapulmonary TB, HIV, and plague. Some of these tests have been brought to market by industrial partners (see below).

[199]BioSpectrum (2011). McEvoy (2012).

[200]Vaidya, D. (2008). Overview on Indian diagnostics market & evaluation of options to play. Presentation.

[201]Tate-Nadkarni, K. (2010). Diagnostics in India; The beginning of a new im "age." *Modern Medicine*, February 18. Available at: http://modernmedicare.co.in/articles/diagnostics-in-india-the-beginning-of-a-new-im-"age"

[202]BioSpectrum. (2011). *BioSpectrum-ABLE biotech industry survey 2011*. (India).

[203]Company websites.

[204]WHO. (2011). Commercial Serodiagnostic Tests for Diagnosis of Tuberculosis [policy statement]. Available at: http://whqlibdoc.who.int/publications/2011/9789241502054_eng.pdf.

[205]Tate-Nadkarni (2010).

[206]Global Fund. (2011). *Quality Assurance Policy for Diagnostics Products*. Report of the Technical Advisory Group. (Geneva). Recent data on Global Fund website. Global Fund PQR database, Available at http://www.theglobalfund.org/en/procurement/pqr/.

Involvement in and Perceptions of Neglected Disease Markets

Infectious diseases are already an important focus for Indian diagnostic firms. The immunochemistry segment, which includes serological tests for infectious diseases, contributes about one-quarter of the Indian market for in vitro diagnostics,[207] and the leading firms sell tests for HIV, malaria, TB, and hepatitis B and C, as well as for more neglected diseases such as dengue, Japanese encephalitis, chikungunya, kala-azar (leishmaniasis), and cholera. Some of the leading firms are exporting infectious disease tests, including HIV and malaria rapid tests, and international donor-funded procurement was attractive to the firms interviewed for this study. This suggests that Indian companies would be willing to develop and market needed new tests for neglected diseases, as long as R&D costs were modest, as would be the case if biomarkers suitable for one of their established platforms were available. When this is the case, development of a new test can be quite cheap—as little as $1 million—even for U.S. firms, largely because testing and regulatory processes for in vitro diagnostics are much less expensive and time-consuming than they are for drugs and diagnostics. The cost of developing a new diagnostic platform can be considerably higher, however. One report estimated the time and cost of developing a new diagnostic test at five years and $20 million.[208]

The lower cost of diagnostic R&D allows firms to consider developing tests for much smaller markets than are considered sufficient for new drugs and vaccines. Even U.S. investors consider a market of $20 million per year to be commercially viable. For this reason, market size is less of an obstacle for neglected disease diagnostic R&D than for drugs and vaccines.

Research and Development Capacity

There is little publicly available information on the R&D capacity of Indian diagnostic firms. Based on our interviews with firms and outside experts, the large manufacturers can develop new tests for established platforms, especially serological rapid tests, as long as biomarkers are available. These firms can then exploit their strengths in low-cost manufacturing. Most of these firms probably have limited expertise in molecular (nucleic acid–based) tests and have not demonstrated the ability to develop innovative platform technologies. In contrast, some of the newer biotechnology companies have developed—or are working on—novel platforms, including some that might be suitable for point-of-care tests. These firms are small and few in number, however, and most have little or no experience in manufacturing.

Thus Indian firms are well-positioned to develop new tests for neglected diseases for which suitable biomarkers are available or can be identified by others. Indian universities and public-sector researchers can contribute in this area, and there are already several examples of successful commercialization by Indian companies of tests developed by the Indian public sector. For example, innovative dengue and hepatitis C tests developed at the ICGEB are being manufactured by J Mitra and XCyton, respectively, and XCyton's Japanese encephalitis test was developed in collaboration with the National Institute for Mental Health and Neurosciences. AIIMS was involved in development of Span's leishmaniasis rapid test, and a test for extrapulmonary TB developed at AIIMS has been licensed to Arbro Pharmaceuticals.

The development of new platforms, including lower-cost versions of existing technologies recently brought to market by foreign firms, will be a bigger challenge. Like the development of innovative vaccines by Indian firms, this will probably require technical assistance from international partners and perhaps collaboration between a smaller, R&D-focused firm and an established manufacturer.

[207]Vaidya, Dheeman. "Overview of Indian diagnostic markets & evaluation of options to play." presentation.

[208]National Institute of Biomedical Imaging and Bioengineering (US) & DBT (India). (2009). Report of the workshop Indo-US workshop on low-cost diagnostic and therapeutic medical Technologies (Hyderabad, India, November).

Research and Development Obstacles

In addition to the obstacles shared by drug and vaccine developers, such as human resources and early-stage financing, diagnostics firms and experts cited some additional challenges.[209]

Indian Regulatory Procedures

Regulatory pathways for approval of in vitro diagnostics in India have been unclear, with some products, including kits for HIV, hepatitis, and syphilis, being defined as "critical" and subject to more stringent requirements. Standards for validation are not clear to companies.[210]

International Product Assessment and Procurement

Although Indian diagnostic manufacturers were interested in donor-funded markets for their products (and some are already participating in these markets), they told us that uncertainty about standards and processes for international procurement were major obstacles for them.

Until 2010, there was no equivalent for diagnostics to the WHO prequalification programs for vaccines and certain drugs, and the quality of malaria rapid diagnostic tests in particular was very variable. WHO has now created a program for diagnostics, which, as of early May 2012, had approved 20 products from five companies.[211] All of the approved products are for HIV or malaria, though the program is also evaluating hepatitis C tests. As of March 2011, applications for 128 products had been received. Curiously, 24 percent of applications were for products made in India, which was more than for any other country, and a further 14 percent were for Chinese products, yet all the currently prequalified products are from companies in Organization for Economic Cooperation and Development countries. It is not clear to what extent this reflects differences in quality, as opposed to the date and completeness of dossiers and other procedural issues.

WHO prequalification is intended, at a minimum, to guide procurement by UN agencies, but it is not yet clear whether it will become, as vaccine prequalification has, a requirement for a broader range of purchasers.

The Global Fund has its own criteria for malaria and HIV rapid tests, as does USAID.[212]

Access to Samples

Access to well-characterized patient samples is crucial to the development and validation of new tests. The need for greater access to samples was raised as an important priority at a meeting of public- and private-sector researchers held at the National Institute of Immunology.[213] WHO, the Foundation for Innovative New Diagnostics (FIND), and the Special Program for Research and Training in Tropical Diseases (TDR) maintain specimen banks for TB, malaria, and sleeping sickness, but the number of kinds of samples may not be adequate for all needs.[214]

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[209]For a discussion of challenges to diagnostics R&D in India, see Ganguly, N. K., Mukhopadhyay, B., Gupta, S. S., & Bharati, K. (2010). *Mapping of Health Products R&D Landscape for Infectious Tropical Diseases in India* (New Delhi: National Institute of Immunology, 40–44). See also Engel, N., Kenneth, J., & Pai, M. (2012). TB diagnostics in India: Creating an ecosystem for innovation. *Expert Rev Mol Diagn 12*: 21–24.

[210]Banarjee, N. S. (2012). India seeks clear regulations on diagnostic kits. *BioSpectrum*, May 28. Available at: www.biospectrumasia.com/biospectrum/regulatory/1386/india-seeks-regulations-diagnostics-kits.

[211]WHO list of prequalified diagnostic products. Available at: www.who.int/diagnostics_laboratory/evaluations/PQ_list/en/index.html.

[212]Global Fund. (2010). Global fund quality assurance policy for diagnostics. Available at: www.theglobalfund.org/en/procurement/quality/diagnostics/#QAPolicy. USAID. (2012). USAID approval process for procurement of rapid HIV diagnostics tests. Presentation at Procuring HIV Diagnostics Tools: Manufacturers, Implementers and Agencies (Geneva: January 31).

[213]Ganguly, N. K., Mukhopadhyay, B., Gupta, S. S., & Bharati, K. (2010). *Mapping of Health Products R&D Landscape for Infectious Tropical Diseases in India* (National Institute of Immunology, New Delhi, India).

[214]For links, see http://globalhealthdiagnostics.tghn.org/articles/specimen-banks/. For details on the TB specimen bank, see Nathanson, C. M., Cuevas, L. E., Cunningham, J., Perkins, M. D., Peeling, R. W., Guillerm, M., Moussy, F., & Ramsay, A. (2010). The TDR Tuberculosis Specimen Bank: A resource for diagnostic test developers. *Int J Tuberc Lung Dis 14*(11): 1461–17.

Conclusions

India's diagnostics industry, like its drug and vaccine industry, has focused historically on supplying low-cost versions of relatively simple types of tests for the domestic market. However, the larger firms have entered export markets, and new biotechnology firms are developing new tests and even new diagnostic platforms. Although the number of innovative firms remains small—and these firms themselves are very small compared to multinational diagnostic companies—the lower costs and typically less-daunting technological and regulatory challenges of diagnostic R&D mean that they may be able to contribute to neglected disease product development. In particular, they are in a good position to develop new rapid tests for diseases where appropriate biomarkers have been identified; there have already been several successful partnerships between Indian public-sector researchers and companies in this area. They may also be able to develop cheaper versions of existing but expensive diagnostic platforms. Finally, in a few cases they may be able to develop new point-of-care platforms.

Crucially, Indian diagnostic firms are interested in many neglected disease markets on commercial grounds. They are likely to require funding for R&D from the Indian government or international donors, however, as well as technical assistance in field validation and in navigating international assessment and procurement processes.

The Indian diagnostics industry may also be able to make an important contribution to the control of non-communicable diseases in India and other low- and middle-income countries by developing affordable tools for diagnosing and monitoring these diseases in low-resource environments.

Case Study: TB Diagnostics

Tuberculosis (TB) kills about 1.5 million people every year; among infectious diseases, only AIDS takes more lives.[215] Incidence is finally beginning to decline, but progress has been slow. India's burden of TB is by far the world's largest, with an estimated 320,000 deaths and 2.3 million new cases in 2010, about one-quarter of the global total.[216] Although India has expanded the reach of its national TB control program, its case detection rate, estimated by WHO at 59 percent, remains low. For comparison, China detects 87 percent of TB cases. Many people in India seek care in the private sector, where the quality of diagnosis and treatment is often poor.

Inadequate diagnostic tools are increasingly recognized as an important barrier to faster progress against TB. In most of the developing world, the standard diagnostic method is sputum smear microscopy, in which trained technicians search for TB bacilli in stained sputum samples. Although microscopy is cheap and specific, it has several deficiencies:[217] It is not very sensitive, failing to detect as many as half of cases of active TB. Moreover, it is relatively slow, requires at least rudimentary laboratory infrastructure, cannot determine drug susceptibility, and performs poorly in HIV patients and children. Alternative diagnostic technologies, notably liquid and solid culture and nucleic acid amplification, address some, but not all, of these deficiencies, and are not always practical in low-resource settings.

[215]WHO. (2011). *Global Tuberculosis Control 2011* (Geneva: World Health Organization).

[216]Ibid., 96.

[217]McNerney, R., Maeurer, M., Abubakar, I., Marais, B., McHugh, T. D., Ford, N., Weyer, K., et al. (2012). Tuberculosis diagnostics and biomarkers: Needs, challenges, recent advances, and opportunities. *J Infect Dis 205*(2):S147–58. Wallis, R. S., Pai, M., Menzies, D., Doherty, T. M., Walzl, G., Perkins, M. D., & Zumla, A. (2010). Biomarkers and diagnostics for tuberculosis: Progress, needs and translation into practice. *Lancet 375*(9729): 1920–37.

Case Study: TB Diagnostics (continued)

At the global level, awareness of the urgent need for better TB tests—and a sense that market forces and existing philanthropic initiatives were not producing results quickly enough—has led several organizations, including Médecins Sans Frontières, Knowledge Ecology International, and the X PRIZE Foundation, to propose large prizes for point-of-care tests that met specific technical criteria as an innovative incentive for new test development.[218] To date, no funder has stepped forward to provide the necessary financing for such a prize.

Although several kinds of new tests would be useful for various purposes, the diagnostic technology that would have the greatest impact would be a truly point-of-care test that could accurately, cheaply, and rapidly detect active TB in peripheral health facilities or even in the community.[219] Tests that perform well in children and in people with HIV and that determine drug susceptibility are also a high priority. Modeling studies estimate that improved TB diagnostics could cut deaths by as much as 36 percent.[220]

TB diagnosis in India, and in many other countries, suffers not only from the deficiencies of microscopy but also from the extensive use of ineffective serological tests. At least 1.5 million serological tests for TB are performed every year in India.[221] This issue reflects weak regulatory oversight of diagnostics in the private sector.

With support from FIND, Cepheid (a U.S. company) has launched GeneXpert MTB/RIF, a cartridge-based molecular diagnostic technology for TB that can also identify the most common kind of drug resistance. This test is more sensitive than microscopy, including in HIV patients, and delivers results in fewer than two hours.[222] It should have an important impact, especially where drug resistance or HIV coinfection is an important problem, and it is being selectively introduced in India. But GeneXpert is expensive—about $17,000 for the machine and $17 for each test cartridge in the public sector—and it requires electricity.[223] Cheaper tests and tests that can be used in remote areas are still needed.[224]

Although the pipeline of new TB diagnostic technologies is growing, big challenges remain. The ideal point-of-care test would be a dipstick-style antibody or antigen assay, similar to those used for HIV or malaria rapid tests. The problem, however, is a lack of biomarkers: no antigen or antibody has been identified that is reliably and specifically associated with active TB.[225] An alternative approach is to make molecular diagnosis of the kind used by GeneXpert cheaper and more accessible in peripheral areas by means of a portable or hand-held device. An advantage of platforms of this type is that they could be designed to test for more than one disease.

[218]For an analysis of these proposals, see Wilson, P. A., & Palriwala, A. (2011). Prizes for Global Health Technologies. (Results for Development Institute, Washington, DC).

[219]Lemaire, J. F., & Casenghi, M. (2010). New diagnostics for tuberculosis: Fulfilling patient needs first. *J Int AIDS Soc 13*: 40. McNerney et al. (2012).

[220]Keeler, E., Perkins, M. D., Small, P., Hanson, C., Reed, S., Cunningham, J., Aledort, J. E., et al. (2006). Reducing the global burden of tuberculosis: The contribution of improved diagnostics. *Nature* (Supplement 1): 49–57. See also www.finddiagnostics.org/programs/tb/need.html.

[221]Morris, K. (2011). WHO recommends against inaccurate tuberculosis tests. *Lancet 377*(9760): 113–14. Grenier, J & Pinto, L., Nair, D., Steingart K., Dowdy, D., Ramsay, A., & Pai, M. (2012). Widespread use of serological tests for tuberculosis: Data from 22 high-burden countries. *Eur Respir J 39*(2):502–05. Jaroslawski, S., & Pai, M. (2012). Why are inaccurate tuberculosis serological tests widely used in the Indian private healthcare sector? A root-cause analysis. *Journal of Epidemiology and Global Health* (in press).

[222]Boehme, C. C., Nabeta, P., Hillemann, D., Nicol, M. P., Shenai, S., Krapp, F., Allen, J., et al. (2010). Rapid molecular detection of tuberculosis and rifampin resistance. New Engl J Med 363(11): 1005–15. WHO. (2011). *Tuberculosis Diagnostics: GeneXpert MTB/RIF Test* [factsheet] (Geneva: World Health Organization).

[223]Evans, C. A. (2011). GeneXpert—A game-changer for tuberculosis control? *PLoS Med 8*(7): e1001064.

[224]Ibid. Denkinger, C. M., & Pai, M. (2012). Point-of-care tuberculosis diagnosis: Are we there yet? *Lancet Infect Dis 12*: 169–70.

[225]Wallis, R. S. & Pai, M., Menzies, D., Doherty, T.M., Walzl, G., Perkins, M.D., Zumla, A., et al. (2010). Biomarkers and diagnostics for tuberculosis: Progress, needs and translation into practice. *Lancet 375*(9729): 1920–37.

Case Study: TB Diagnostics (continued)

Academic and public-sector researchers are probably in the best position to find new TB biomarkers; the Gates Foundation has recently funded a number of new projects.[226] But the development of a cheap, point-of-care molecular diagnosis platform will require the involvement of industry. A number of promising technologies are in development.[227]

Although many of the new diagnostics technologies that have received international attention are being developed by U.S. and European biotechnology firms, Indian firms, especially the new breed of more innovative firms, may also be in a position to contribute to the development of new TB tests. A conference in Bangalore in August 2011 brought together TB experts, Indian diagnostic firms, and officials of the government TB control program to discuss the types of tests that are needed in India; features of the public- and private-sector markets for TB diagnostics; and ways that government, academia, and industry could work together to accelerate development of improved tests.[228]

The potential market for a new TB test is large enough to be commercially attractive to Indian diagnostic firms: a preliminary analysis presented at the Bangalore meeting estimated this market at about $75 million per year, which is about evenly divided between the public and private sectors.[229] Indian diagnostic companies interviewed for this project agreed that the market is commercially attractive. Moreover, the global market for TB tests is quite large: a 2006 WHO report estimated that $300 million was then spent every year on TB testing in low- and middle-income countries, and that the number of tests performed annually could rise to 193 million by 2020.[230] Scientific obstacles, rather than small markets, have probably been the main deterrent to industrial investment in new TB tests.[231]

A number of Indian firms are already involved in TB diagnostics. Many of the larger firms produce serological tests. Several firms are developing new tests, however. Perhaps the most promising project currently underway in India is a joint venture between Bigtec Labs and the Tulip Group to develop a nucleic acid–amplification device that could be used in peripheral settings.[232] Bigtec has been developing tests for several other diseases using this platform and is reportedly close to launching a TB test that would be battery-powered and less expensive than GeneXpert, but that would not test for drug resistance and would require a separate instrument for sample preparation.[233] No data have been published on the performance of the new instrument, though validation studies are underway. The joint venture with Tulip (Molbio Diagnostics) is a way to combine the innovative capacity of a small biotech with the manufacturing and marketing experience of an established diagnostic supplier.

[226]Bill and Melinda Gates Foundation. (2012, February 9). Gates Foundation invests in cutting-edge research to diagnose tuberculosis in developing countries [press release].

[227]Niemz, A., Ferguson, T. M., & Boyle, D. S. (2011). Point-of-care nucleic acid testing for infectious diseases. *Trends Biotechnol 29*(5): 240–50. Pai, N. P., & Pai, M. (2012). Point-of-care diagnostics for HIV and tuberculosis: Landscape, pipeline, and unmet needs. *Discov Med 13*(68): 35–45.

[228]Engel, N., Kenneth, J., & Pai, M. (2012). TB diagnostics in India: Creating an ecosystem for innovation. *Expert Rev Mol Diagn 12*: 21–24. Pai, M. (2011). Diagnosing tuberculosis: Can India take the lead? *PloS Med* blog available at: http://blogs.plos.org/speakingofmedicine/2011/09/28/diagnosing-tuberculosis-can-india-take-the-lead.

[229]Bakshi, A. (2011). Business case of investing in TB diagnostics in India. Presentation at TB Diagnostics in India: From Importation and Imitation to Innovation (Bangalore, August 25–26). This estimate has been subsequently updated, with a new estimate of $200 million per year (Madhukar Pai, personal communication, June 17, 2012).

[230]WHO. (2006). *Diagnostics for Tuberculosis: Global Demand and Market Potential* (Geneva: World Health Organization).

[231]Interviews and analysis conducted for an R4D report on prizes, *Prizes for Global Health Technologies* (2011).

[232]Bigtec website, available at: http://www.bigteclabs.com/index.html. Lee, J. F. (2012). The power of knowing. TB Online website, available at: www.tbonline.info/posts/2012/4/11/power-knowing.

[233]Interview with Chandrasekhar Nair, founder and director of Bigtec, May 3, 2012.

Case Study: TB Diagnostics (continued)

Bigtec has received funding from CSIR's NMITLI program (see Annex 1) and from Grand Challenges Canada.

Several other Indian firms have potentially relevant technologies or projects.[234] It is worth noting that a number of these projects involve collaborations between Indian universities and firms, though firms interviewed for this project voiced complaints about working with public-sector partners similar to those heard from drug and vaccine firms.

- XCyton has launched a polymerase chain reaction–based test that can identify a number of pathogens, including TB, in a single sample. This product was developed in collaboration with Indian research partners and with support from the NMITLI program. It is currently intended to quickly determine the cause of acute infections in hospitalized patients.
- Achira Labs, a recent start-up in Bangalore, is developing a multiplex point-of-care diagnostic platform based on microfluidics, as well as an innovative technology using hand-woven silk "chips." Achira is currently focusing on applications of its technology to thyroid diseases and infertility; use of the technology for TB would depend on the availability of suitable biomarkers. Achira has also won funding from Grand Challenges Canada.
- Arbro, a contract research organization, has signed an agreement to commercialize several TB diagnostic technologies developed at the All India Institute of Medical Sciences in Delhi. The consortium is supported by DBT.
- Span, one of the larger diagnostics firms, is working with Delhi University on TB rapid tests.
- Bisen Biotech is collaborating with Jiwaji University in Madhya Pradesh to develop a TB test based on TB-specific glycolipids. This project is supported by DBT.
- Xcelris Labs has signed a deal with Epistem, a U.K. biotech, to distribute a new handheld molecular test in India. Xcelris does not seem to be involved in the development of this product, which is expected to reach market in 2012.

Indian academic and public-sector researchers are also actively involved in TB diagnostics research. In addition to the projects listed above, several of which originated with or involved public-sector researchers, it is worth mentioning recent work at ICGEB on the possibility of diagnosing TB through volatile organic compounds present in urine.[235] ICGEB has been awarded a grant from the Grand Challenges Canada program and the Gates Foundation to further develop the concept of an "electronic nose" for TB diagnosis.

Our analysis suggests that there are at least five ways that Indian researchers and firms can contribute to the development of new TB diagnostics.[236]

[234]This information comes from company websites, presentations at the Bangalore meeting, and interviews with company executives in August 2011.

[235]Banday, K. M., Pasikanti, K. K., Chan, E. C., Singla, R., Rao, K. V., Chauhan, V. S., & Nanda, R. K. (2011). Use of urine volatile organic compounds to discriminate tuberculosis patients from healthy subjects. *Anal Chem 83*(14): 5526–34.

[236]Funding awarded under the Grand Challenges scheme and the Bill and Melinda Gates Foundation. (2012). Available at http://www.icgeb.org/news_English/items/icgeb-new-delhi-tb-research.html.

Case Study: TB Diagnostics (continued)

- **Identification of novel biomarkers by academic and public-sector researchers**
- **Development and low-cost production of a rapid test using a conventional point-of-care platform**, if and when a suitable antigen or antibody biomarker is identified. This would be a natural role for Indian industry, which already produces a broad range of serological tests.
- **Development and production of a cheaper, follow-on version of the GeneXpert technology**, if patents do not pose insuperable barriers. This might also be a good fit for Indian industry, with its strengths in reverse engineering and low-cost production. But Cepheid's machine undoubtedly incorporates a great deal of proprietary know-how, which may make imitation difficult. The Gates Foundation has expressed interest in supporting such a follow-on product, though it is not necessarily focusing on Indian manufacturers.[237]
- **Development of a new point-of-care diagnosis platform**. Creating, testing, and manufacturing a new platform is expensive and challenging, but the new or forthcoming products from XCyton and Bigtec/Tulip suggest that it is not beyond the capacity of Indian firms.
- **Field trials.** Rigorous trials will be critical to WHO endorsement and international procurement of a new test, and trials in India will be important to adoption by the Indian public sector. Indian firms may need technical and financial assistance to design and carry out these trials. FIND evaluated GeneXpert in 1,730 patients in three countries.[238]

Indian firms and their academic collaborators face several challenges in bringing new TB tests to market, in addition to the scientific and technological obstacles.

- **Early-stage funding.** Start-ups—such as Achira Labs—may play a larger role in the development of new diagnostic technologies than of new drugs or vaccines. But Indian entrepreneurs with promising new technologies hoping to start new companies face the shortage of early-stage capital in India (see Section 2). Once a company has been in existence for a few years, it has access to funding from the Indian government, and promising TB diagnostics projects should be able to attract support from international sources.
- **Patient samples.** The WHO and the Special Programme for Research and Training in Tropical Diseases (TDR) maintain a TB specimen bank.[239] Bigtec has apparently used this bank to test its new machine. However, lack of specifically Indian samples has been identified as an obstacle to development of a test for the Indian market.[240]
- **Lack of clear signals on product priorities from the national TB control program.** Although the Indian market is attractive to Indian firms, these firms do not know what kind of product the public sector would buy or what standard of performance a product would have to meet.

[237]Interviews with Gates Foundation officials.

[238]Boehme, C. C., et al (2010). Rapid molecular detection of tuberculosis and rifampin resistance. *N Engl J Med 363*(11): 1005–15.

[239]Nathanson, C. M., Cuevas, L. E., Cunningham, J., Perkins, M. D., Peeling, R. W., Guillerm, M., Moussy, F., & Ramsay, A. (2010). The TDR Tuberculosis Specimen Bank: A resource for diagnostic test developers. *Int J Tuberc Lung Dis 14*(11): 1461–67.

[240]Pai, M. (2011). Diagnosing tuberculosis: Can India take the lead? *PloS Med* blog, available at: http://blogs.plos.org/speakingofmedicine/2011/09/28/diagnosing-tuberculosis-can-india-take-the-lead.

Case Study: TB Diagnostics (continued)

- **Breaking into the private market.** The private sector market for TB diagnostics is large and growing, but as the success of poorly performing serological tests shows, there is no guarantee that an improved new test would quickly win a large market share.
- **Unclear Indian regulatory standards.** The ban on serology tests for TB may lead to a more rigorous system for validating all in vitro tests, which would give product developers clearer standards to aim for.
- **Lack of clarity on international regulatory and procurement processes and standards.** An accurate, affordable, point-of-care TB test could have large markets outside India, including donor-funded markets. But Indian firms do not have a clear sense of international processes for evaluating, recommending, and procuring new diagnostic tests.

Most of these obstacles can be overcome with appropriate policy reforms, some of which are already under way. We conclude that India is in an excellent position, with international support, to make important contributions to the development of badly needed new TB tests.

CHAPTER 6
CONCLUSIONS AND RECOMMENDATIONS

6 Our analyses of the Indian drug, vaccine, and diagnostics industries support several general conclusions.

First, these industries are growing rapidly. Although the advent of TRIPS and the opening of the Indian economy to greater foreign competition and ownership have forced important changes in business models, Indian firms have continued to thrive and move into new product areas. This growth has been driven both by the expansion of the Indian market, which Indian firms have so far continued to dominate in most areas, and by a big increase in exports, especially by drug and vaccine companies.

Second, although the success of Indian firms in all three segments is still primarily built on efficient production of follow-on (in the case of drugs, generic) rather than highly innovative products, the R&D capacity of Indian industry has unquestionably grown. The leading vaccine companies have moved from producing basic vaccines to developing their own versions of more sophisticated vaccines and have built capacity in biotechnology. The drug industry now has expertise in aspects of modern drug discovery, as well as clinical trials, though this expertise is increasingly deployed on a contractual basis for international clients rather than to advance new drug candidates owned and funded by Indian firms. Diagnostic companies have developed conventional immunological tests for infectious diseases, sometimes in collaboration with Indian universities and research institutes, and some are beginning to move into molecular diagnostics.

Third, despite this progress, Indian R&D capacity still lags well behind that of U.S.- and Europe-based multinationals in important respects. No new chemical entity has been brought from discovery through to market in India, and no firm has the technology or resources to carry out high-throughput screening of large molecular libraries. The industry's expertise is still greatest in chemical synthesis and manufacturing process development. No new class of vaccines has been developed by an Indian firm, and the industry has little experience with the large clinical trials required to license a truly new vaccine. No Indian company has demonstrated that it can develop a new diagnostic platform, though some promising technologies are in the works.

These weaknesses stem in part from remaining deficiencies in the larger innovation system. Although there are excellent scientists in the Indian public system, ties between public-sector researchers and industry are still weak, and relatively few products originating in Indian universities or public-sector research institutes have reached market. Indian universities produce large numbers of scientists and engineers, but shortages of people with the skills required for industrial R&D and of good research managers are still constraints. According to some experts, a culture of innovation is still not well developed, and Indian regulators lack experience in evaluating new products.

Although new government programs are helping to fill the financing gap at early and middle stages of product development, private risk capital is in short supply for new biomedical R&D firms. Even the largest drug and vaccine firms would be hard-pressed to finance the most expensive late-stage clinical trials for some

new drugs and vaccines without help from international partners. The Indian government has launched a number of initiatives to address these weaknesses, but in some cases, it will take years before their impact is clear.

Another important constraint is scale. Indian drug, vaccine, and diagnostic firms are still many times smaller than the leading multinationals, which limits their ability to finance R&D and to spread R&D risk across a broad portfolio of projects and candidate products. The biotechnology industry is growing, but the number of companies pursuing new technologies is still small.

Fourth, Indian industry is becoming increasingly integrated into international markets and into a global R&D system, through buyouts of Indian firms by multinationals, purchases of U.S. and European firms by Indian companies, R&D partnerships and contracting out of R&D tasks, and interpenetration of markets.

Although these conclusions apply to a considerable degree across the industry, there are important differences among the three segments that have implications for neglected disease product development. These differences stem from intrinsic features of the medical technologies, from differences in regulatory pathways, and from differences in markets and industry structure.

- Although a number of Indian drug firms have gained access to U.S. and European markets for their generic drugs, no Indian vaccine has yet won regulatory approval from either the U.S. FDA or the European Medicines Agency. (This is partly because there is no generic pathway for vaccines: each company must independently demonstrate to regulators the safety and efficacy of its product.) As a result, Indian vaccine companies have remained focused on markets in India and other developing countries, including the GAVI/UNICEF market; this emphasis is reflected in their R&D priorities. In contrast, the large Indian drug firms are increasingly focused on products with global markets, mostly for noncommunicable diseases.
- In recent years, access to lucrative markets for generic drugs, as well as the formidable challenges of drug R&D, has moved many large Indian drug firms away from investment in new drug development. Indian vaccine firms, in contrast, are continuing to strengthen their R&D capacity and to move toward more innovative products.
- Although the major Indian drug firms have scaled back new drug R&D for their own portfolio and focused on generics and new formulations and delivery mechanisms, a growing contract research industry offers both clinical trial and earlier-stage services. This work is naturally focused on the product priorities of clients based in high-income countries.
- Integration of Indian firms into global markets is more advanced in the drug industry in other ways as well. There have been more important acquisitions of Indian drug firms by multinationals, as well as more acquisitions of foreign firms by the big Indian companies.
- Most of the leading Indian vaccine and diagnostic companies are privately held, in many cases by founders or their families, whereas all of the biggest drug producers are now publicly traded. Although this is difficult to prove, it is our impression that being privately held has given some of the vaccine companies greater freedom to include noncommercial considerations in their portfolio decisions. Family ownership does not guarantee an orientation to public health needs, of course, and there is no certainty that the values of company founders will survive leadership transitions. State control is another way to insulate product choices from commercial pressures and to undertake development of needed health technologies with limited revenue potential. The involvement of state-owned Indian manufacturers in drug and vaccine R&D has declined, but Indian Immunologicals has a growing pipeline of projects focused on neglected diseases. It remains to be seen whether it can bring these mostly early-stage projects to market.

- Finally, there are crucial differences among the product classes in the cost and difficulty of developing and winning regulatory approval for new technologies. In general, new in vitro diagnostics are cheaper, easier, and quicker to develop than drugs or vaccines, though this depends on the availability of biomarkers and suitable platforms. Truly new (first-in-class) drugs and vaccines are challenging and in most cases still beyond the capacity of Indian firms, at least without substantial financial and technical assistance. Follow-on vaccines (products based on the same concept as existing vaccines) are in general less difficult, as are incremental or adaptive innovations in both drugs and vaccines, such as new presentations and combinations.

Implications for Neglected Disease Research and Development

What do these findings mean for India's role in the development of new drugs, vaccines, and diagnostics for neglected diseases?

The first and perhaps most important point is that Indian industry is already making significant contributions to new health technology development. Indian vaccine companies have brought to market follow-on versions of existing vaccines—most recently, pentavalent combination vaccines that have made supply to GAVI-eligible and other developing countries more secure and affordable. These companies are now developing a number of additional vaccines, of which rotavirus vaccines are the closest to market, that should bring similar benefits. Indian companies have developed fixed-dose combinations of HIV drugs and rapid diagnostic tests for malaria, as well as for several neglected tropical diseases.

We believe that this contribution is likely to grow, though with limitations and differences among product types.

The ability of Indian vaccine companies to develop new vaccines should continue to advance. And because of the natural focus of these companies on infectious diseases, their continued reliance on developing-country markets, as well as their willingness to pursue markets of modest size by multinational corporation standards, much of this increased capacity will be devoted to the development of products of public health importance in low- and middle-income countries. Markets matter for these firms, too, and in general, they will not invest in products for the most neglected diseases—that is, those that do not promise either large-scale, donor-subsidized international purchase or significant private markets in India and other middle-income countries. In addition, their ability to contribute to the development of truly new and scientifically challenging vaccines, such as those against malaria, TB, and HIV, is still limited, though they may be able to help in certain defined areas. Finally, they will probably need both technical and financial assistance for some time in bringing to market even some of the more challenging follow-on vaccines, such as those against rotavirus, pneumonia, and HPV.

Although India's drug firms are larger and in some ways more sophisticated than its vaccine companies, they seem less likely to contribute to neglected disease R&D, for two main reasons. For one, many of these firms are withdrawing from earlier stages of R&D and refocusing their investments on incremental R&D related to their profitable generics businesses. More important, the industry is increasingly focused on global and especially high-income markets and becoming more integrated with the multinational pharmaceutical industry through acquisitions and partnerships. The net result of these trends, which will almost certainly continue, is that the leading drug companies seem no more interested in products for neglected diseases than are the multinationals. Cost advantages in certain areas of R&D may offer an opportunity for international organizations, such as the drug product development partnerships (PDPs), to carry out some neglected disease drug development in India on a contractual basis, just as multinational firms are outsourcing some aspects of drug R&D to India.

The diagnostic industry is more difficult to characterize, but many firms are still focused on infectious disease and on the Indian and developing-world markets. Coupled with the much lower costs of diagnostic R&D, this presents a promising opportunity for Indian firms to contribute to the development of needed new tests for neglected diseases. There seem to be more successful partnerships between public-sector researchers and Indian firms in diagnostics than in drugs and vaccines, and DBT is investing in many promising diagnostic projects. In fact, diagnostics may present some of the best opportunities for India to make new contributions to neglected disease product development.

Several trends are likely to nourish, but also eventually limit, India's ability to play a special role in the development of new health technologies for the needs of developing countries. First, R&D capacity will surely continue to grow, though it will remain behind that of the leading multinational firms for some time. This presents an opportunity, but may also move firms toward a focus on products that promise returns sufficient to cover R&D costs. Second, R&D costs in India will continue to grow with capacity, as economic growth and international mobility narrow salary differences, eroding at least some of the cost advantages India currently enjoys in some areas. In addition, international integration will continue, with more and more interpenetration of markets, acquisitions in both directions, R&D and manufacturing partnerships, and, probably, increasing similarities in corporate culture and business models. Finally, it is possible that the special character of some Indian firms will fade as more family-owned firms become publicly traded companies.

Taken together, these trends imply that there may be *a limited window of opportunity* for Indian industry to make a special contribution to global health R&D, when it has the capacity to develop new technologies but before its distinct strengths and commercial orientation are lost to integration in a truly global pharmaceutical and biotechnology industry. Taking advantage of this opportunity will require balancing health and industrial policy objectives. We discuss below some ways in which both the Indian government and international partners could support neglected disease product development in India and ensure that India's growing R&D capacity is deployed at least in part toward public health needs. We note here a valuable paper by Rezaie and Singer, which argues that economic and public health objectives for India's pharmaceutical and biotechnology industry can be reconciled.[241]

Opportunities for the Indian Government and International Partners

Given this state of affairs and its likely evolution, how can the Indian government or international organizations interested in global health technology development make the best use of Indian health R&D capacity to serve the needs of the poor, not only in India but also in other developing countries?

In some cases, Indian industry can be engaged in new product development on a commercial basis by clarifying the types of products needed and making public or donor-subsidized markets more predictable, transparent, and attractive. The advent of GAVI has unquestionably prompted Indian firms to develop new vaccines, and the Global Fund has driven the development of fixed-dose combinations of HIV drugs and malaria and HIV rapid tests. For diagnostics, greater clarity on international quality standards and approval processes would help. For its part, the Indian government could stimulate the development of some types of products—for example, new TB tests—by clearly spelling out what kinds of new products it would like to procure for public-sector programs, as well as by clarifying its own product approval procedures. There is little doubt that expressing some willingness to pay more than the lowest possible prices for new products—for example, by relaxing price controls on

[241]Rezaie, R., & Singer, P. A. (2010). Global health or global wealth? *Nat Biotechnol 28*(9): 907–09.

drugs—might make the public-sector market more attractive to potential product developers. This must be balanced against access and budgetary considerations, however, and it is politically challenging.

Clarifying new product needs and procurement processes will not be sufficient for many products, as markets for some will still be too small to be commercially attractive to Indian firms, and others will be beyond their capacity to develop without help. In these cases, financial support or technical assistance, from either the Indian government or international partners, will be required. The support of the DBT, the U.S. NIH, and the Gates Foundation for the development of the rotavirus vaccine candidate that Bharat hopes to bring to market is a good example of this kind of partnership, as was the collaboration between the Meningitis Vaccine Project and Serum Institute. In some cases, the government of India or an international donor may have to bear the bulk of late-stage development costs. Such an arrangement will not make sense for all needed products. If Indian firms do not have the necessary skills or infrastructure, it may be more efficient for international organizations interested in development of specific products to work with an industrial partner in the U.S. or Europe.

Even when Indian firms are unwilling or unable to bring a product to market, even with financial and technical help, there may be cost or other advantages to carrying out some specific tasks in India on a contractual basis, just as multinational companies increasingly outsource some aspects of R&D to India. Such an arrangement implies that some entity is assuming overall responsibility for directing and financing development of the needed technology. This entity could be the Indian government or an international donor-funded PDP.

Finally, in cases where industry cannot be engaged on a suitable basis, it may make sense to expand the role of the public sector in product development. The long-term trend away from public-sector manufacturing of drugs and vaccines is unlikely to be reversed, but the public sector will continue to play an essential role, both in basic and applied research and in building the innovation ecosystem and filling financing gaps. This role is inevitably larger for neglected disease products that are less interesting to industry.

Implications for Other Emerging Economies

To what extent do our findings hold for other developing countries with well-developed pharmaceutical and biotech industries and substantial innovative capacities, such as China and Brazil? As we have not studied these countries in detail, we will limit ourselves to a few general remarks.

- Many of the broad trends occurring in India are affecting China and Brazil as well, especially growing integration into international markets, growing domestic markets that are very attractive to multinational pharmaceutical and vaccine companies, and potential conflict between industrial policy and public health objectives for domestic R&D.
- India, China, and Brazil differ considerably in their strengths and weaknesses in pharmaceutical and biotechnological R&D. India still leads in chemistry and in meeting international production standards, whereas China is now stronger in many areas of basic science, including biology.
- China has made a very large investment in the R&D ecosystem as a whole, and most observers expect that investment to bear fruit in health technology development.
- At least in vaccines, both production and new product development remain mostly in the public sector in both Brazil and China. In addition, portfolio decisions are closely tied to the needs of the national immunization program, especially in Brazil.

Limitations and Areas for Further Work

This study has tried to address a broad range of technologies, institutions, and elements of the Indian innovation system. Perhaps inevitably, the study's treatment of many important issues is relatively preliminary and, in many cases, largely qualitative. It would be useful to be able to bring more quantitative data, as well as additional interviews, to bear on some of these issues.

We would also like to strengthen our treatment of the public sector, both as a site of basic and applied research that could be commercialized in collaboration with industry and as a product developer in its own right. We focused mostly on for-profit firms, because in most areas of health technology, these firms now account for the majority of late-stage product development in India. In addition, at least according to the firms we interviewed, the technology they bring to market tends to come from international sources rather than the domestic public sector. However, the growth of the private sector is happening in parallel with efforts to strengthen public-sector research, and a better understanding of current capacity, trends, and perspectives of public-sector researchers would provide important balance.

There are several other areas in which we would like to build on this initial, landscaping study. First, we hope to build a stronger case for our findings and recommendations in a few specific areas. One such area is the relationship between Indian government procurement, including procurement through the new health insurance schemes, and R&D priorities, government financing of R&D, and commercial investment in new product development. Second, we hope to analyze to what extent certain globally discussed policy ideas for supporting neglected disease product development, such as prizes, patent pools, or innovative regulatory pathways, might be useful in India and how they might be adapted to the Indian context. Third, we have focused here on products for infectious diseases. We hope to explore the contribution that India and Indian industry can make to the development of locally adapted and cost-effective health technologies for noncommunicable diseases.

Specific Recommendations for Supporting Neglected Disease R&D in India

Financing

- Expand collaborative funding of neglected disease R&D by international partners through existing Indian government windows. International donors have the flexibility to support high-risk work and start-up companies and can also support projects important to populations outside of India.
- Explore the potential of "impact investing," especially in diagnostics.
- Continue and diversify international financial support for expensive late-stage trials of products that have substantial global public health potential.

Technology Transfer and Technical Assistance

- Continue to provide technical assistance to Indian firms developing needed vaccines, as well as financial support for large trials. Expand similar support for needed diagnostics.
- Facilitate partnerships between U.S. and European academic researchers working on neglected diseases and Indian firms
- Use international "technology hubs" as alternatives to one-on-one transfer for some technologies. The WHO technology hub for flu vaccines and NIH licensing of rotavirus vaccine technology are possible models.
- Make available "open source" diagnostic platforms on which Indian firms could develop tests.
- Establish sample banks for key diseases from which diagnostic researchers and product developers could draw.
- Fund publicly available intellectual property landscaping studies in key technology areas, such as HPV vaccines.

- Provide a range of support services to start-up firms that have a neglected disease focus, perhaps through an international platform like the proposed Global Health Accelerator.[242]

Demand Aggregation and Market Signals

- Adopt and publicize clear criteria for new product procurement by the Indian government.
- Improve consultation between public health and research arms of the government on priority products in order to harmonize R&D support with public procurement.
- Support disease burden and cost-effectiveness studies by government institutes—or by nonprofit groups with government endorsement—to inform decisions on new technology adoption.
- Expand aggregation of global demand for important health technologies.
- Use donor volume guarantees or price subsidies for certain products with small markets (pediatric formulations, second-line TB drugs, and drugs and diagnostics for neglected tropical diseases).

Regulation

- Harmonize and clarify international standards and guidance for new products, especially diagnostics. Expand the WHO prequalification program for diagnostics.
- Assist Indian firms with new products to navigate international regulatory and procurement processes.
- Develop a "fast track" regulatory pathway in India for technologies with significant potential public health impact.
- Strengthen the regulation of diagnostics in the private sector to create stronger incentives to develop and supply more effective tests.

Measures to Strengthen the Health Innovation System as a Whole

As described in Section 2, Indian firms point to a number of broad challenges to conducting and expanding their R&D efforts. These challenges apply to both neglected disease and more commercially oriented R&D and are beyond the scope of this report. However, the success of efforts to address these challenges will have important implications

for neglected disease R&D, and we are following with interest the initiatives of DBT, DST, CSIR, ICMR, TDB and other arms of the Indian government in a range of important areas, including university research, science education, regulatory processes, infrastructure, links between public-sector researchers and industry, and public financing of private-sector product development. Some of these initiatives are described in Annex I.

[242]Frew S. E., Liu, V. Y., & Singer, P. A. (2009). A business plan to help the "global South" in its fight against neglected diseases. *Health Aff 28*(6): 1760–73.

ANNEXES

Annex I: Government Initiatives to Support Pharmaceutical and Biotechnology R&D

In 2007, the government of India (GOI) revamped its National Biotechnology Development Strategy and allocated more funding for programs supporting public-private partnerships.[243] These funding schemes provide direct funding for private R&D. The most prominent programs for pharmaceutical and biotechnology R&D are detailed below.

Biotechnology Industry Partnership Program (BIPP). BIPP is a funding initiative under the management of Biotechnology Industry Research Assistance Council (BIRAC) of the Department of Biotechnology (DBT) that aims to promote innovation of national importance, pre proof-of-oncept research and biotechnology development in agriculture and health through public-private partnerships. BIPP was launched in 2008 with $75 million to disburse over five years.[244] It provides government cost-sharing arrangements for "futuristic" technology projects (this scheme will not support incremental innovation). BIPP divides the projects it will fund into the following four categories:[245]

Category 1: Partnership for fulfilling major unmet technological needs

Category 2: Partnership for increasing India's global competitiveness in technology

Category 3: Partnership for evaluation and validation of existing high-priority products

Category 4: Development of core shared research and technology facilities

BIPP provides a combination of loans and grants to firms. Support does not usually exceed 50 percent of costs, though high-value clinical trials can receive up to 75 percent of costs (both depend on the level of national importance).[246] In general, support is between 5 and 50 crore rupees, and DBT collects 5 percent royalties on sales of technology produced through grants up to twice the amount of the original grant. Most firms opt for royalty-free, low-interest loans.[247] Of the 53 projects, BIPP has supported so far, 58 percent have focused on health, and seven of those target neglected diseases.

Drugs and Pharmaceutical Research Programme (DPRP). The DPRP is a program of the Department of Science and Technology (DST) that intends to increase India's drug development capacity and support the development of products that meet India's health

[243]Frew, S. E., Kettler, H. E., & Singer, P. A. (2008). The Indian and Chinese health biotechnology industries: Potential champions of global health? *Health Aff 27*(4): 1029–41.]

[244]Singh, S. (2009). Building public-private research partnerships in troubled times. *Cell 136*: 987–89.

[245]Department of Biotechnology. (2010). Biotechnology Industry Partnership Programme (BIPP). Available at: http://dbtindia.nic.in/BIRAP/BIPP%20-%20Proposal%20Submission.pdf.

[246]Ibid.

[247]Vijayraghavan & Dutz (2012).

[248]Department of Science and Technology. Drugs and pharmaceutical research. Available at: www.dst.gov.in/scientific-programme/td-drugs.htm#1.

needs.[248] This is one of the few technology-funding programs dedicated exclusively to health. Between 2004 and 2009, approximately 16 percent of its projects were oriented toward neglected diseases.

New Millennium Indian Technology Leadership Initiative (NMITLI). NMITLI is a popular program of the Council of Scientific and Industrial Research (CSIR) that began in 2001. This program supports projects that establish India's leadership role in technology. In addition to reviewing project requests, the board actively seeks out promising projects that align with areas of national importance and invites them to participate.[249] The program provides grant support to public institutions and low-interest loans (3–5 percent) to private partners.[250] It emphasizes supporting high-risk projects that may be unable to procure funding from other mechanisms. NMITLI will also cofinance projects alongside venture capitalists. In 2009, its budget was expanded by an additional 700 crore rupees, allowing the program to spend about $267.9 million until 2012.[251]

Small Business Innovation Research Initiative (SBIRI). In 2005, DBT launched SBIRI, an initiative that supports high-risk pre–proof-of-concept research and late-stage development in small and medium science-based companies with fewer than 500 employees. Program objectives include commercializing publicly generated technology, meeting societal needs, and building the R&D capabilities of small firms. SBIRI is managed by the Biotechnology Industry Research Assistance Council (BIRAC). Firms can apply for support independently or in partnership with a public institute. Based on the total funding needed and the stage of research, support takes the form of both grants and low- (or no-) interest loans. Thus far, the program has mostly provided loans, which companies have about 10 years to repay.[252] For phase I projects, grants can support 80 percent of costs for projects up to $55,000; for projects up to $219,000, grant support can cover 50 percent.[253] Companies can also apply for interest-free loans for large projects. Phase II projects can be supported through loans up to $2.2 million.[254] Resulting health products are supposed to be available at concessionary prices on the Indian market, and the intellectual property (IP) is co-owned by DBT and the innovator. According to a breakdown of successful applicants as of January 2011, 20 percent of the supported projects relate to health, and about 5 percent of the projects pertain specifically to neglected diseases.

Technology Development Board (TDB). The TDB was established under the Department of Scientific and Industrial Research (DSIR) in 1996 to encourage the commercialization of indigenous technology in any technology-based field. Healthcare constitutes the greatest share of its agreements, and many biotech firms have benefited from its support.[255] The board provides equity, soft capital loans, and grants to companies for a maximum of three years. The majority of its agreements are for debt financing.[256] The TDB has the option to retain royalty-free licenses on IP that results from its funding. Between 1996 and 2008, the program was authorized to disburse 501.42 crore rupees (about $114.7–141.6 million).[257]

[248]Department of Science and Technology. Drugs and pharmaceutical research. Available at: www.dst.gov.in/scientific-programme/td-drugs.htm#1.

[249]Government of India (GOI) *New Millennium Indian Technology Leadership Initiative: A Public-Private-Partnership R&D Programme* (New Delhi: Council of Scientific and Industrial Research).

[250]GOI. *Stepwise Procedure for Developing Industry Originated Projects Under NMITLI* (New Delhi: Council of Scientific and Industrial Research).

[251]Press Information Bureau. (2009, February 23). New Millennium Indian Technology Leadership Initiative scheme expanded.

[252]Vijayraghavan and Dutz (2012).

[253]GOI. Small Business Innovation Research Initiative for Public Private Partnership (New Delhi: Department of Biotechnology). Available at: http://dbtindia.nic.in/uniquepage.asp?id_pk=136.

[254]Ibid.

[255]GOI. (2008). *Annual Report, 2007–2008* (New Delhi: Technology Development Board).

[256]Ibid.

[257]Ibid.

Most public programs have a mandate to support projects that are critical to the country's health needs, but it is not clear how this mandate drives resource allocation. Eligibility for these programs, with the exception of the SBIRI, requires certification of a company's R&D unit by the DSIR. SBIRI allows for DSIR certification after a project has been approved.

In addition to the existing programs that have been discussed, the GOI may launch additional initiatives to support R&D in the near term. The latest National Vaccine Policy suggests that the DBT will create a Grand Challenges program focused on high-priority vaccines.[258] The GOI and state-level governments are also working to expand the availability of biotechnology parks and improve the country's innovation infrastructure.

[258]GOI. (2011). *National Vaccine Policy* (New Delhi: Ministry of Health and Family Welfare).

Annex II: Government Agencies Involved in the Regulation of Health Technologies in India

In India, the Central Drugs Standards and Control Organization, which falls under the purview of the Ministry of Health and Family Welfare, houses the Drug Controller General of India and plays a coordinating role in setting regulatory guidelines and coordinating regulatory activities for health technologies. However, a number of agencies and groups that fall under other departments of government are also involved in the regulation of health technologies. The system and interactions between these groups are complex and vary by the type of technology in consideration. The main bodies involved in regulation are detailed below.

The main act governing the regulation of drugs and clinical trials is Schedule Y of the Drugs and Cosmetics Act. Approval for the research and use of new biotechnologies is directed by the Biosafety Rules under the Environmental Protection Act and complemented by the Biotechnology Safety Rules issued by the Department of Biotechnology.[259]

Agency	Regulatory Duties
Central Drugs Standards and Control Organisation	Sets clinical trial guidelines, reviews technologies entering the country, oversees Good Manufacturing Practices (state-level authorities are involved in actually inspecting facilities and identifying substandard drugs).
Drug Controller General of India[260]	Responsible for all drug and health technology regulation (licensing and so on), currently including recombinant products.
Indian Council of Medical Research (ICMR)[261]	Registers contract research organizations and all clinical trials. Its institutes are often involved in the coordination and implementation of trials, provide support to trial implementers for Good Clinical Practice guidelines, and lay out clinical research guidelines (though no mechanism exists to enforce compliance[262]).

[259]Reddy, V. K. I. (2009). Biotech Regulation in India: Problems and Promises. *Biotechnology Journal 4*: 306–09.

[260]Jeffery, R., & Santhosh, M. R. (2009). Architecture of drug regulation in India. What are the barriers to regulatory reform? *Journal of Health Studies 11*: 13–32.

[261]Woodman, A., &Gupta, S. Is India evolving to support global drug development? *Raj Pharma* (January).

[262]Phadke, A., & Srinivasan, S. (2010). *Strengthening the Drug Regulatory Mechanism in India*. Draft note for the Working Group on Drugs and Food Regulation for Giving Inputs for the 12th Five Year Plan. (New Delhi: Government of India).

ANNEX II: GOVERNMENT AGENCIES

Agency	Regulatory Duties
Department of Biotechnology (DBT)[263]	Involved in the regulation of all biotechnology projects (including agriculture) and manages the Review Committee on Genetic Manipulation. It has been authorized to set up a single independent agency to regulate all biotech products, though this process is still underway. Once operational, the agency will be responsible for regulating genetically modified organisms with applications in human and veterinary health, including the regulation of recombinant biologics, such as DNA vaccines, recombinant gene therapy products, recombinant and transgenic plasma-derived products like clotting factors, and veterinary biologics. However, it will exclude all other therapeutic proteins derived from recombinant organisms, which will continue to be regulated by the Drug Controller General of India.
Department of Pharmaceuticals[264]	Involved in setting pricing controls.
Committee for Control and Supervision of Experiments on Animals[265]	Must approve all experiments involving animals.
Genetic Engineering Approval Committee	The Ministry of the Environment and Forest coordinates this committee, but it includes members from the DBT, Ministry of Industrial Development, Department of Ocean Development, Department of Science and Technology, ICMR, and others to approve of all products related to genetic engineering.
Other	State-level authorities are involved in regulating pharmaceutical manufacturing facilities. The Atomic Energy Review Board and the Baba Atomic Research Centre assist in reviewing trials and equipment involving radiation or radiopharmaceuticals.[266]

[263]GOI. (2008). *Draft Establishment Plan for the National Biotechnology Regulatory Authority* (New Delhi: Department of Biotechnology, Ministry of Science and Technology).

[264]Jeffery, R & Santosh, M.R. (2009) Architecture of Drug Regulation in India: What are the Barriers to Regulatory Reform? *Journal of Health Studies* II: 13-32.

[265]Kumar, V., & Muthuswamy, V. (2000). *Use of Animals in Scientific Research* (New Delhi: Indian Council of Medical Research, Government of India).

[266]Jayasheel, B. G. (2010). Carrying out clinical trials in India. *Raj Pharma* [regulatory feature].

Annex III: People Interviewed

Name	Title	Affiliation
Dhananjaya Dendukuri	CEO	Achira Labs
Satya Dash	COO	Association of Biotechnology-Led Enterprises
Sai D. Prasad	Project Manager, Rotavirus Vaccine Project; Vice President, Business Development	Bharat Biotech International
Chandrasekhar Nair	Director and CEO	Bigtec Laboratories
Gene Walther	Deputy Director of Diagnostics	Bill and Melinda Gates Foundation
Peter Small	Deputy Director of Tuberculosis	Bill and Melinda Gates Foundation
Mahima Datla	Senior Vice President	Biological E. Limited
Saman Habib	Head, Division of Molecular and Structural Biology	Central Drug Research Institute
Harkesh Dabas	Director, New Initiatives	Clinton Health Access Initiative
Bhaven Sampat	Assistant Professor	Columbia University
Zakir Thomas	Project Director, Open Source Drug Discovery Initiative	Council for Scientific and Industrial Research
Michael Tsan	Associate Partner	Dalberg Global Development Advisors
Billy Stewart	Senior Health Advisor, India	Department for International Development, UK
Bindu Dey	TB Advisor	Department of Biotechnology, India
Maharaj K Bhan	Secretary	Department of Biotechnology, India
Shreemanta K Parida	CEO, Grand Challenges	Department of Biotechnology, India

ANNEX III: PEOPLE INTERVIEWED

Name	Title	Affiliation
Mark Perkins	Chief Scientific Officer	Foundation for Innovative New Diagnostics
Jaideep Moitra	Vice President for R&D	Gennova Biopharmaceuticals
Sanjay Singh	CEO	Gennova Biopharmaceuticals
Achin Gupta	Senior Vice President of Corporate Strategy	Glenmark Pharmaceuticals
Anjali Nayyar	Senior Vice President	Global Health Strategies
Rajat Goyal	India Country Director	International AIDS Vaccine Initiative (IAVI)
Wayne Koff	Chief Scientific Officer	IAVI
Ramesh Matur	General Manager of R&D	Indian Immunologicals
V. A. Srinivas	Research Director	Indian Immunologicals
Rishikesh Krishnan	Professor of Corporate Strategy	Indian Institute of Management, Bangalore
Sudip Chaudhari	Professor of Economics	Indian Institute of Management, Calcutta
Dilip Shah	Secretary General	Indian Pharmaceutical Alliance
Tahir Amin	Cofounder and Director	Initiative for Medicines, Access and Knowledge
Szymon Jaroslawski	Postdoctoral research fellow	Institute of Bioinformatics and Applied Biotechnology
Chetan Chitnis	Principal Investigator, Malaria Group	International Centre for Genetic Engineering and Biotechnology
Vir Chauhan	Director	International Centre for Genetic Engineering and Biotechnology
Leonard P. Ruiz	President and Director	International Medica Foundation
Shrikant Kulkarni	Vice President of Exports	Lupin
Ashley Birkett	R&D Director	Malaria Vaccine Initiative
Madhukar Pai	Associate Professor	McGill University
Penny Grewal	Director of Global Access	Medicines for Malaria Venture

ANNEX III: PEOPLE INTERVIEWED

Name	Title	Affiliation
Nirmal K Ganguly	Distinguished Biotechnology Research Professor	National Institute of Immunology
Sanjukta Sen Gupta	Scientist III	National Institute of Immunology
Roger Glass	Director	National Institutes of Health, Fogarty International Center
Ashu Sikri	Investment Analyst	Omidiyar Network
Jasjit Mangat	Director of Investments, Head Access to Capital	Omidiyar Network
Tanjore Balganesh	Distinguished Scientist	Open Source Drug Discovery
Zakir Thomas	Project Director	Open Source Drug Discovery
Georges Thiry	Head of rotavirus vaccine development project	Program for Appropriate Technology in Health (PATH)
John Boslego	Director of Vaccine Development	PATH
Sonali Kochhar	Clinical Research and Drug Development Specialist	PATH
Lysander Menezes	Health Systems Design Specialist	PATH
Tarun Vuj	Country Director, India	PATH
Rajiv Gulati	President of Global Pharmaceuticals Business	Ranbaxy Laboratories
Sridhar Ramanathan	Executive Director of Operations	ReaMetrix
Rajeev Dhere	Senior Director	Serum Institute
Suresh Jadhav	Executive Director	Serum Institute
Harish Iyer	CEO	Shantha Biotec
Pradip Desai	Founder, Chairman, and Director	Span Diagnostics
Vijay Chandru	CEO	Strand Life Sciences
Kas Subramanian	Chief Science Officer	Strand Life Sciences
Dheeman Vaidya	Director of Business Operations and Customer Excellence	Stryker
William Wells	Director of Market Access	TB Alliance

ANNEX III: PEOPLE INTERVIEWED

Name	Title	Affiliation
Neeraj Mohan	Executive Director	The Blackstone Group
Natarajan Sriram	Director	Tulip Group
Chad Gardner	Program Director of Global Health Research	UBS Optimus Foundation (formerly Global Forum for Health Research)
Rahim Rezaie	Postdoctoral research fellow	Asia Pacific Foundation of Canada
Shirshendu Mukherjee	Strategic Advisor, India R&D Initiative	Wellcome Trust
Keshav Deo	Vice President of Chemical Research	Wockhardt
Mandar Kodgule	Associate Vice President and Head of Intellectual Property and Strategic Planning	Wockhardt
Mark Dutz	Senior Economist, Private-Sector Development, South Asia Region	World Bank Group
Martin Friede	Scientific Officer	World Health Organization, Vaccine Research Unit
Banda Ravikumar	Chairman and Managing Director	XCyton Diagnostics

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