

Pharmaceutical R&D for Low-Income Countries

Global Trends and Participation by Indian Firms

Has the current portfolio of public, non-profit and private sector research initiatives, together with the extension of stronger intellectual property rights, been associated with any discernible change in broad based measures of R&D activity targeted at poor country markets? This paper is a follow-up to a 2001 baseline study of existing and historical R&D patterns and it revisits and updates the statistical series and reports on a second wave of R&D activity by Indian pharmaceutical firms. Taken as a whole, the various data sources examined in the paper point to a steady increase in pharmaceutical inventive activity in some areas of specific interest to developing countries. The set of diseases still in need of better low-cost treatments has seen a trend increase in its share of patenting and bibliometric citation. While overall investment in pharmaceutical R&D in India surged over the past five years, it became less targeted towards the health needs of the developing world.

JEAN O LANJOUW, MARGARET MACLEOD

It has now been over 10 years since the “TRIPS” Agreement was signed – requiring all members of the newly-formed World Trade Organisation (WTO) to implement a set of minimum standards for intellectual property protection.¹ Significantly, one of the required standards was that countries must grant pharmaceutical researchers at least 20 years of protection on both the discovery of new molecules and on new methods of manufacture (product and process protection). The inclusion of intellectual property standards in the treaty establishing the WTO was deeply unpopular with the developing countries and the source of considerable friction during the negotiations. At the time, many poorer countries offered weak or no protection on pharmaceuticals. These countries worried that the introduction of patents would require them to pay higher drug prices, and some were also concerned that patent restrictions would limit a local generic industry’s ability to prosper by imitating the newest drugs. During the TRIPS negotiations, however, proponents offered a number of reasons for why the developing countries might, in fact, benefit from the introduction of product patents. High levels of intellectual property (IP) protection, it was suggested, would encourage multinationals to market their newer pharmaceuticals more quickly and extensively in the developing world; the offer of strong IP protection would encourage local and multinational firms to establish R&D centres there, promoting technological development; and finally, perhaps the most compelling argument was that raising the intellectual property standards in the developing world would give private firms an incentive to invest in the development of products of specific importance to consumers in those countries.²

The latter was a plausible argument. While it has been possible for developing countries to free-ride on products developed for rich country markets, they have a subset of pharmaceutical needs that differ from those in the developed world (see Section I). To address these specific demands, any market-based incentives

must come primarily from the developing world. Survey and other empirical evidence suggest that patent protection plays a key role in providing R&D incentives for the pharmaceutical industry, so one could expect TRIPS-related reforms to make a difference to the amount of investment targeted at poor country markets [e.g. Cohen et al 2000].

Indeed for several reasons the reforms associated with TRIPS initially appeared to provide a rather unique opportunity to examine the R&D stimulus provided by patents. The reforms represent an unusually large change in the IP regime, affecting the bulk of the world’s population and a sizeable and growing pharmaceutical market. Because the countries introducing protection have drug needs that are identifiably different from the countries that had had protection for some time, one could look for changes in the allocation of research expenditures as a result of the strengthening of the patent system. Changes in patterns of investment are considerably easier to detect and ascribe to a policy reform than are changes in overall levels of investment. Finally, a useful feature of the policy reform from the point of view of analysis was that it was exogenous to the affected countries. They fought the TRIPS agreement and were put under pressure to accede to it; and the timing was driven by the wider trade treaty negotiation process.

In an effort to examine the possible R&D stimulus effect of TRIPS, shortly after the treaty was signed Lanjouw and Cockburn initiated a study of existing and historical R&D patterns to serve as a baseline against which to consider changes in the following years. The results of that study are summarised in Lanjouw and Cockburn (2001). This paper is the first follow-up to the study. We revisit and update the statistical series presented in the earlier study and report on a second wave survey of R&D activity by Indian pharmaceutical firms.

Before turning to the data, however, we discuss in Sections II and III how the R&D stimulus has evolved since TRIPS was

signed. In the earlier paper, Lanjouw and Cockburn (2001) pointed to a variety of “confounding events” that looked at the time as though they might dilute or enhance the effect of patent law reform on R&D choices or alter R&D patterns directly, thereby making inferences about the reforms difficult. In the intervening years some of the most important of these confounding factors became considerably more significant. With regard to the stimulus value of new patent rights, there have been political developments that could not fail to have profoundly affected firms’ expectations about their freedom to profit from patent rights in poorer countries. Meanwhile we have seen a remarkable variety of non-patent based initiatives to boost R&D investment on products related to the developing world. As a result, the reforms to the global patent regime centred on the TRIPS Agreement can no longer be viewed as a clean experiment for examining firm responses to strengthening patent protection. On the other hand, the experiment has been cluttered precisely because the world began to focus more of its attention on how to direct pharmaceutical research investment towards the neglected health problems of the poor. In light of this, it remains interesting and important to ask whether the current portfolio of public, non-profit and private-sector research initiatives, together with the extension of stronger IP rights in a non-receptive environment, have been associated with any discernible change in broad-based measures of R&D activity.

I Pharmaceuticals Specific to Developing Country Markets

The disease patterns and drug demands of the group of countries introducing patent protection differ in two ways from those of the countries that have had such protection for some time. Because of the substantially lower incomes and often difficult climates of the countries undertaking IP reforms, the optimal characteristics of drug therapies for these markets differ. In interviews, directors of R&D in Indian firms pointed out that an important part of their development work when adapting western drugs to the Indian market involved improving products’ stability characteristics so that they would retain their efficacy longer on pharmacy shelves, and survive rougher transport conditions and extended periods of time out of cold storage (personal interviews, Lanjouw). There will also be a stronger preference for relatively low-cost therapies in poor countries even though they might be less effective.

The second difference between the two groups of countries is in their disease patterns. Many diseases are global in nature and their therapies have worldwide markets (e.g., cancer, heart disease, diabetes). Others primarily afflict people living in the poorer countries. Table 1 lists all of the diseases for which 99 per cent or more of the estimated global burden was in low- and medium-income countries as defined by the WHO in 2002. The global burden of a disease is based on the disability adjusted life years, or DALYs, lost to the disease. DALYs attempt to capture both the impact of long-term disability and premature death [WHO 1996]. Note that this is not a ranking of the most important diseases in the developing countries in terms of total disease burden, but rather those that are specific to developing countries. This is the distinction we are after for the purpose of trying to pick up changes in R&D investment in response to new

patent rights in those countries and to other targeted R&D policy initiatives.

II Evolution in the System of Global Patent Protection for Pharmaceuticals

The TRIPS Agreement was the culmination of an extended effort by the multinational pharmaceutical industry and supportive governments to strengthen patent regimes in the developing world. Beginning as far back as the early 1980s the United States has pursued this agenda in aggressive bilateral negotiations. In 1984, Congress passed a revision of the Trade and Tariff Act, which authorised the US government to take retaliatory action against countries failing to give adequate protection to intellectual property (Section 301). This was strengthened in 1988 with legislation mandating that each year the US trade representative identify countries without adequate protection. The resulting pressure convinced several countries to change their patent laws regarding pharmaceuticals as part of larger reforms to their intellectual property rights systems. For example, Korea introduced protection in 1986; Mexico passed new laws in 1991; and Brazil passed legislation to allow pharmaceutical product patents in 1996. The 1993 North American Free Trade Agreement (NAFTA) included an agreement to grant full protection to pharmaceutical product innovations, while the TRIPS Agreement itself came into effect in January of 1995.

The fact that there were earlier incidences of patent reform makes the timing of change in research incentives somewhat imprecise. Further, the TRIPS Agreement also allowed some developing country signatories a grace period for adjustment to the new standards. India, the most significant example, only began to examine pharmaceutical product patent applications as of January 2005. Countries with a grace period were, however, still required to accept product patent applications (the “mailbox” provision) and to offer “exclusive marketing rights” to any

Table 1: Diseases of Low- and Middle-Income Countries, 2002

Disease	Lower-Income Country Share of Total DALYs Lost	DALYs Lost	Annual Deaths (Thousands)
Chagas Disease	100.0	667	14
Dengue	100.0	616	19
Diphtheria	100.0	na	5
Lymphatic Filariasis	100.0	5,777	0
Malaria	100.0	46,486	1,272
Onchocerciasis-river blindness	100.0	484	0
Polio	100.0	151	1
Trichuriasis	100.0	1,006	3
Trypanosomiasis	99.8	1,525	48
Ascariasis	99.8	1,817	3
Japanese Encephalitis	99.8	709	14
Leishmaniasis	99.8	2,090	51
Schistosomiasis	99.8	1,702	15
Syphilis	99.8	4,200	157
Tetanus	99.8	7,074	214
Diarrhoeal Diseases	99.5	61,966	1,798
Leprosy	99.5	199	6
Measles	99.4	21,475	611
Trachoma	99.4	2,329	0

Note: DALYs are estimates of years of life lost or lived with a disability, adjusted for its severity.

Source: World Health Organisation, *The World Health Report 2004*, Statistical Appendix Tables 2 and 3.

Available at: <http://www.who.int/whr/2004/annex/en/>.

inventor with a patent in a WTO member country and marketing approval for the new drug in his home market. This effectively created partial protection in those countries beginning in 1999, and thousands of patent applications made since that date are now emerging from the mailbox. Given the staggered nature of these changes, it is most accurate to think of pharmaceutical patent rights extending in developing countries over a period of time beginning from the mid-1990s and continuing through 2000, rather than at a specific moment.

As important as dating legal changes in patent codes and procedures is interpreting whether the recent patent law reforms represent a real change in R&D incentives in the eyes of potential investors. If patents are to change private investment behaviour, firms must expect that future rights will be respected and effectively enforced. They must also believe that they will be able to use patent-based control over the marketing of innovative products to obtain attractive profit margins. Absent this, patent rights cannot provide an R&D stimulus. It is significant, then, that the new patent rules in developing countries are being introduced and tested in what has become a very highly-charged environment. Many events on the world stage during the past five years could give potential patent holders good reason to be sceptical about the future value of holding patents in lower-income countries.

Examples include:

– In 1998, 39 multinational pharmaceutical companies brought suit against the South African government, asserting that a proposed amendment to the South African medicines law was inconsistent with that country's TRIPS obligations. After coming under intense criticism for this widely publicised action, and having lost the support of their home governments, the companies felt compelled to withdraw the case in April of 2001 [‘t Hoen 2002].

– In February of 2001 the WTO established a dispute panel to rule in response to a US complaint about features of Brazilian patent law. The US charges focused on local working provisions that it claimed were in violation of the TRIPS Agreement. Again in the face of fierce criticism from NGOs and other advocates, the United States decided to drop the complaint in June of that year.

– In November 2001, the WTO ministerial conference meeting in Doha adopted a “Declaration on TRIPS and Public Health”, which reaffirmed countries' ability to issue compulsory licences of patents on pharmaceuticals to serve the interests of public health.³ It was also agreed that the least developed countries would not have to implement or enforce pharmaceutical product patents until 2016.

– In 2003 the South African Competition Commission ruled against GlaxoSmithKline and Boehringer-Ingelheim in a case charging the firms with setting excessive prices on patented products and refusing to license generic competitors. The firms agreed to license generic production as part of a settlement to prevent the case from moving to a higher tribunal.

– Since the late 1990s the media and vocal and active advocacy groups have insisted on a link between corporate use of patent rights and restricted access to anti-retrovirals and other drugs needed to confront the HIV/AIDS crisis in the developing world. Responding to the barrage of negative publicity, the industry has felt compelled to proclaim loudly and repeatedly that it does not patent in poor countries nor make use of patent rights to raise prices there.⁴

That said, some more recent events could have given firms

greater confidence that the extension of patents might hold value for them:

– On August 30, 2003, the TRIPS Council came to an agreement allowing exports under compulsory licence to countries without manufacturing capacity. Although extending the right to export, the complexity of the terms agreed and lack, so far, of implementation by member governments could be viewed as encouraging to R&D investors.

– The current wave of US free trade agreements all include chapters reinforcing TRIPS or requiring even higher IP standards, and also including explicit protections for pharmaceutical test data. Having test data protection conveys market exclusivity similar to a medium-length product patent because of the prohibitive cost of repeating clinical trials. Unlike patents, data protection has, so far, been unencumbered by provisions for compulsory licensing.

– In January 2005 India reached the end of its grace period and implemented full pharmaceutical protection in compliance with TRIPS. That this major player would ultimately comply was not obvious 10 years ago when the Agreement was originally signed.

For the purpose of understanding R&D investment what do these developments mean? Most importantly, if we do not see a noticeable shift in R&D towards the particular needs of developing country markets now or over the next years this could have two interpretations. It could mean that the patent regime is never going to be an effective R&D stimulus for these countries because they are too poor. In other words, that the original argument in support of TRIPS was not correct. But it could also mean that, while the system could be effective in principle, it is failing because the patent “rights” in question have been sapped of meaning. That is, in the existing political environment patents in poor countries do not provide an R&D incentive.

III

Other Incentives to Invest in Drug Research Related to the Developing World

Side by side with the changes in the global IP system, there has been a remarkable increase in concern about global health issues and especially infectious disease in high-income countries. This process had already begun by the mid-1990s when the TRIPS was agreed, the spread of HIV/AIDS and drug resistant organisms for once easily treated diseases having created an “intense public interest in ‘emerging and re-emerging’ diseases” [WHO 1996].

Since then, yet further attention has been drawn to the issue for two powerful reasons. First, extensive news coverage has confronted people in the developed world with the human tragedy unfolding in poor countries ravaged by HIV/AIDS. The tie-in to global trading rules and corporate behaviour has made the health crisis an even more effective news story. Other diseases have also grabbed the headlines. In 2003 a global outbreak of the viral respiratory illness Severe Acute Respiratory Syndrome (SARS) touched people around the globe in days. Less dramatically, West Nile virus continues its march across the United States. No one can feel completely safe from diseases that burden the poor.

With the September 11th terrorist attacks in New York city and the introduction of anthrax into government buildings in Washington DC, the potential for bioterrorism has become a second powerful source of concern. It has generated a new sense of urgency to address the potential spread of infectious diseases.

These concerns have translated into greater funding in recent

years to support research targeting global infectious disease. The US National Institutes of Health (NIH) Revitalisation Act of 1993 formally added “tropical diseases” to the National Institute of Allergy and Infectious Diseases (NIAID) mission statement in recognition of its role as the primary source of funding for US civilian investigators conducting research in areas of tropical medicine (NIAID 1997). One would expect any increase in support for targeted public-sector research to be seen there. Table 2 gives NIH budget figures for tropical disease research over the past decade. It is broken into three sub-periods because of changes in the definition of the relevant research. In real terms, spending on tropical diseases increased only 8.7 per cent from 1990 to 1995, and did not increase at all as a share of the total NIH budget. Between 1996 and 1999 real spending increased by 9 per cent and fell as a share of all spending. However, between 2001 and 2004 real spending grew almost fivefold, and increased from 1 to over 4 per cent of the entire NIH budget.⁵

In July 2004, US president Bush signed into law “Project BioShield”, described as a comprehensive effort to develop and make available modern effective drugs and vaccines to protect against attack by bioweapons (e.g. smallpox, anthrax, Ebola, plague).⁶

The heightened awareness and concern about tropical and infectious diseases has also led to many new R&D initiatives directed at discovering and developing vaccines and pharmaceutical treatments for diseases specific to poor countries [see Lanjouw and MacLeod 2005, for examples].

IV Statistical Trends in R&D Indicators

In this section we examine trends in indicators of R&D activity. New research could be done by both private and public sector researchers. We first consider trends in grants dispersed by the NIAID as an indirect measure of the direction of pharmaceutical researchers’ interests. We then look at trends in citations to the biomedical literature, which should be a relatively early indicator of R&D activity. Next we consider patenting in the US – the most direct signal of commercial interest in an area of research. In the last two sections we focus on Indian R&D – both US patenting by India-based scientists and the results of an R&D survey. One might expect scientists working in India to have a comparative advantage in developing drugs targeting developing country markets and thus that new R&D activity would be most apparent there.

National Institutes of Health – Grant Awards

Extramural grant decisions at the NIH might be influenced both by changes in the focus of private or public sector researchers. Interviews at the NIH suggested that there are three ways in which a change in the diseases of interest to private firms could affect the direction of NIH grant funding (personal interviews, Lanjouw). The first is directly – some grants are the result of CRADA or SBIR submissions by private firms.⁷ The second is that company representatives sit on NIH advisory councils and ad hoc working group panels. If firms would like to see more basic research done on malaria host immune responses, for example, they can press for this in these settings. In response, NIH might put out a corresponding request for application (RFA) in which the specific interest is articulated. RFAs represent only a small share of

extramural grants, however, so this route is limited. The third route is through growing industry/academic research links. The industry increasingly engages with academic researchers through collaborative research [Cockburn and Henderson 1998]. This is likely to influence the direction of academic research, and hence the characteristics of the extramural grant proposals submitted to NIH by academics: the “researcher initiated”, or RO1, grants.

NIH maintains a comprehensive database, known as CRISP, containing federally-funded research grants made by the US Public Health Service. The bulk of these are awards made through and administered by the NIH itself, with a small number originating with the Centres of Disease Control, the Food and Drug Administration and other government agencies. As noted, the majority of these grants support research conducted at universities, hospitals and research institutes, with smaller numbers of awards received by private sector organisations, either directly through the granting process or under CRADAs or the SBIR programme. Intramural NIH research projects are also reported, but not the amount of the award. Projects include clinical research as well as basic science, and awards for training and infrastructure development.

As we do in part of the analysis of worldwide patenting and citation trends discussed below, we focus on research grants directed at (or at least mentioning) malaria. Table 3 shows the total number of “malaria” projects identified in the CRISP file and their total funding, in current and real dollars for fiscal years 1975-2002. A “malaria” project is one found by searching project titles and descriptions for a list of relevant keywords: malaria, malarious, plasmodium, falciparum, vivax, etc. Not all of the research projects selected by this search strategy are exclusively focused on malaria, and some may just be trying to maximise support for their proposal by listing as many applications of the research as possible, but we have no basis to believe that these

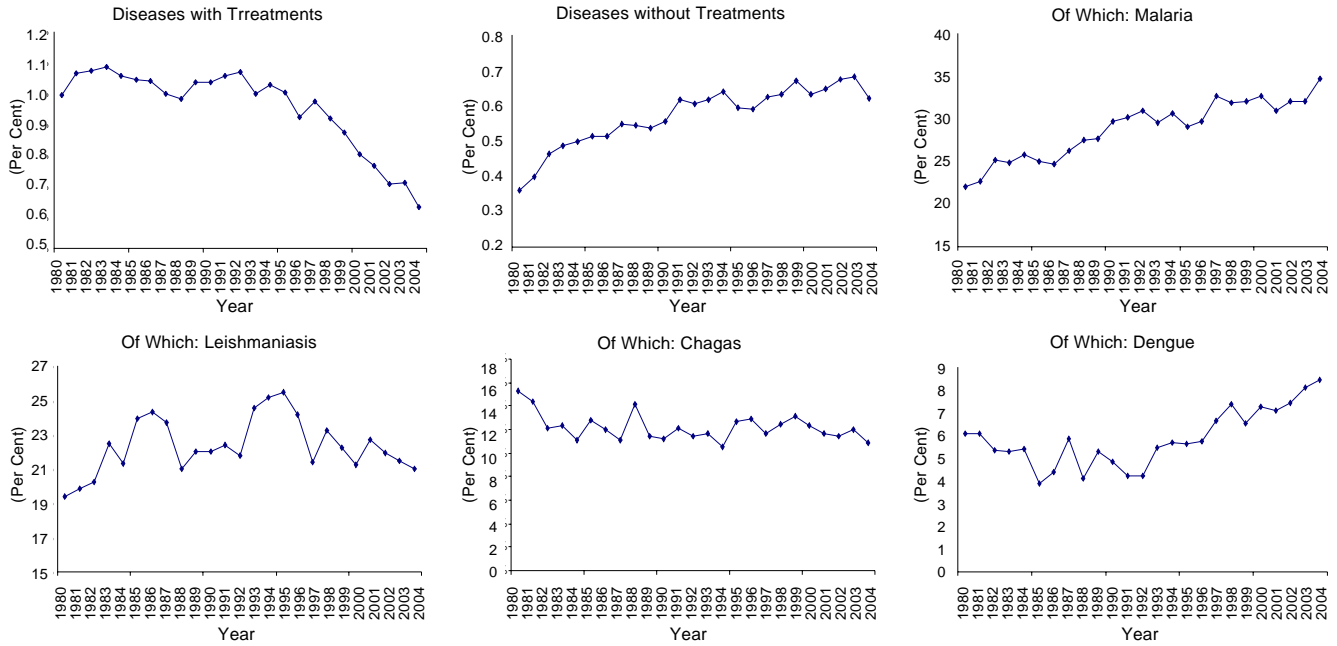
Table 2: Budget Allocations to Tropical Disease Research at the National Institutes of Health
(Millions of 2000 dollars)

Year	NIAID Tropical	Other Institutes Tropical	Total Tropical in 2000 Dollars	Pct Growth in Total over Previous Year	Tropical as Pct of Total NIH	Pct Growth in Share of Tropical
1990	38.4	6.5	64.4	–	0.53	–
1991	39.5	7.8	64.7	0.5	0.51	(3.8)
1992	43.6	8.4	68.1	5.3	0.52	2.0
1993	36.9	10.1	59.6	(12.6)	0.46	(12.5)
1994	41.3	12.2	65.3	9.6	0.49	7.7
1995	44.2	15.2	70.0	7.3	0.52	6.8
1996	90.4	18.1	124.7	–	0.91	–
1997	97.2	16.9	127.6	2.3	0.89	(2.2)
1998	104.0	17.9	131.9	3.3	0.89	(0.3)
1999	125.4	17.7	149.3	13.2	0.91	2.7
2000	164.7	20.0	184.7	23.7	1.04	13.3
2001	129.1	93.4	213.5	–	1.08	–
2002	114.2	108.2	206.0	(3.5)	0.96	(11.6)
2003	926.2	117.0	923.3	348.3	3.90	306.8
2004	1,070.10	120.8	1015.5	10.0	4.28	9.8

Notes: (i) There was a change in the definition of “tropical” beginning in 1996. Then, from 2001, the “tropical diseases” breakdown was no longer generated and was replaced by “Emerging Infectious Diseases”, including those important to biodefence. For 2002-04 we have removed total spending on anthrax and smallpox to arrive at numbers corresponding more closely to the original class of tropical diseases.
(ii) Values for 2004 are estimated. Currency is converted to real 2000 dollars with the NIH R&D Price deflator (BRDPI).

Source: Lee Pushkin, Office of Budget, the National Institutes of Health (personal communication).

Figure 1: Bibliometric Citations



sources of bias change systematically over time. To normalise these figures we use the total number of awards and the overall budget of the NIAID.

Until 1997, the CRISP database contained descriptions of research projects, the amount of funds awarded, plus subject indexing terms. From 1998 the award amounts were dropped from the public database. To circumvent this reduced transparency in the later years required two steps. First, we identified grants related to malaria using a keyword search in the CRISP database. Then we matched these identifiers to state-by-state data on grant award.⁸ Unfortunately, this is an imperfect process, as grant spending is not always reported by state contractors to the NIH office that maintains these records (Katerina Pearsons, NIH, personal communication). It means that the dollar figures for 1998 and onward are underestimates. Thus, we indicate a break in the time series in Table 3 between 1997 and 1998. Trends in the numbers of grants related to malaria should be unaffected by the change in information reporting, but trends in funding should not be carried over the break.

The total NIAID budget and the total number of NIAID administered grants are given in the first two columns of Table 3. Columns three to five indicate the total funds and numbers of grants awarded in each fiscal year that were related to malaria. The last two columns give the trends for grants related to malaria normalised by total NIAID activity.

There was an almost eightfold increase in the number of NIH grants related to malaria between 1975 and 2002. During this period there was also strong growth in the number of grants overall, but those related to malaria more than doubled even relative to total NIAID administered grants. The increase in grant numbers is most apparent in the late 1980s, and again in the mid-1990s. The award values for grants related to malaria have also increased relative to NIAID grant funding overall. There was some increase in the late 1980s. It is unclear what happened in the mid- to late 1990s because of the reporting shift. However, since the values reported here for malaria funding in the most

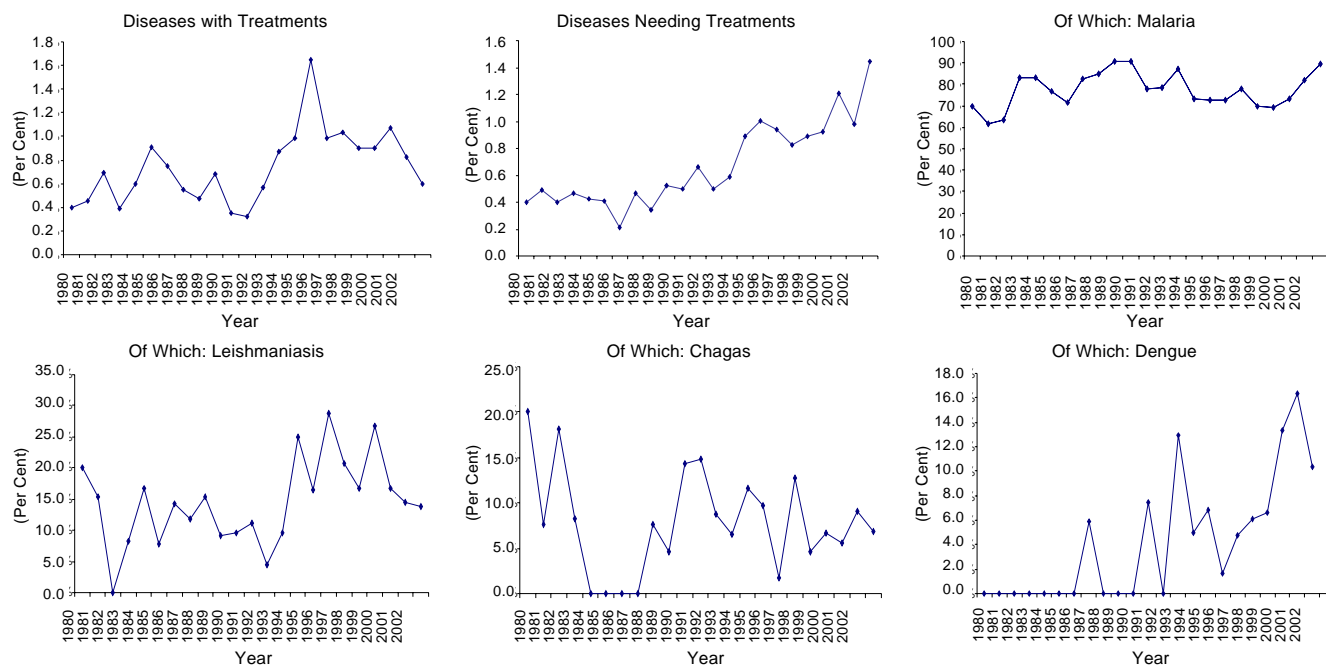
recent years are underestimates, there has clearly been a significant trend upward in the share of NIH research dollars devoted to this disease through the extramural grant process.

Table 3: National Institutes of Health Grant Allocations

Fiscal Year	NIAID* Total		Malaria Projects		Malaria as a Pct of NIAID		
	Research		Total	2000			
	(millions)	Grants	Funding (thousands)	Dollars	Funding	Grants	
1975	119	1,685	2,355	9,125	47	1.98	2.68
1976	126	2,069	6,540	23,581	90	5.19	5.57
1977	140	1,623	3,730	12,456	45	2.66	3.15
1978	162	1,751	3,425	10,649	44	2.11	2.91
1979	191	2,035	5,418	15,554	64	2.84	3.54
1980	215	2,150	5,445	14,240	71	2.53	3.66
1981	232	2,193	4,402	10,426	62	1.90	2.95
1982	236	2,203	5,198	11,335	62	2.20	2.90
1983	279	2,339	5,496	11,283	65	2.17	2.84
1984	320	2,445	7,110	13,779	81	2.93	3.40
1985	370	2,593	9,590	17,596	87	2.59	3.44
1986	367	2,537	12,863	22,651	105	3.50	4.35
1987	545	2,848	14,668	24,527	122	2.69	4.49
1988	639	3,106	22,159	35,284	145	3.47	4.98
1989	740	3,232	23,373	35,379	148	3.16	4.80
1990	831	3,677	27,973	40,119	164	3.37	4.87
1991	906	3,857	22,147	30,301	172	2.44	4.82
1992	960	3,823	25,878	33,910	149	2.70	4.29
1993	984	3,798	28,983	36,724	178	2.95	4.90
1994	1,064	4,200	39,448	48,121	227	3.71	6.04
1995	1,093	4,028	45,663	53,838	242	4.18	6.51
1996	1,171	4,721	43,216	49,682	223	3.69	5.83
1997	1,258	4,884	-	-	221	-	5.29
1998	1,352	5,142	45,563	49,291	274	3.37	5.33
1999	1,565	5,335	50,569	52,759	264	3.23	4.95
2000	1,777	5,270	82,227	82,227	300	4.63	5.69
2001	2,041	5,249	87,446	83,917	342	4.28	6.52
2002	2,340	5,435	94,858	87,860	372	4.05	6.84

Notes: (i) Funding totals and grant numbers drawn from CD-based CRISP records until 1997. From 1998 onwards, malaria funding represents aggregate grant values for extramural grants matching the CRISP malaria records: <http://crisp.cit.nih.gov> keywords "malari%| falciparum | plasmodium | vivax | ovale".
(ii) Teaching and fellowship grants are not included.
(iii) Prices are deflated by the NIH R&D Price deflator (BRDPI).
(iv) The fiscal year runs to September.
* National Institute of Allergy and Infectious Diseases Mission.

Figure 2: US Patent Counts



Bibliometric Citations

A broader avenue for picking up worldwide changes in research investment in tropical diseases is through publications in the scientific literature. We extracted data on publications from the online PubMed database of bibliographic information drawn primarily from MEDLINE, PREMEDLINE and molecular biology databases.⁹ These databases include citations from approximately 4,800 current biomedical journals published in the US and 70 other countries. We cannot distinguish in these data between publications by private researchers and those by public or academic researchers, but as discussed above, because of collaborative research an increasing interest in tropical diseases on the part of industry due to new patent rights is likely to influence research publications more broadly. Researchers in all sectors might be motivated by the types of initiatives described in Section III.

We compile citation counts using search words for target diseases and, within each disease count, for the subset of citations also making reference to a drug therapy or vaccine. Search words are similar to those used for the patent data described below. The main difference is that the malaria search is narrower here and includes citations with references with the root word malari*. The data were collected for each year 1980 through 2004. The trends over time are presented in Figure 1 and some of the specific citation counts are given in Table 4.

Our focus disease categories represent a very small percentage of total biomedical research as evidenced by the presence of these keywords in journal articles. Taken together, references to the set of tropical diseases were found in just 1.25 per cent of all citations in 2004.

Because gaps in scientific knowledge or the absence of useful treatments also affect research priorities, we break the diseases in Table 1 into two groups: those for which there is a reasonably good, low-cost, treatment or vaccine available today, and those for which further progress is needed.¹⁰ The first two panels in Figure 2 display the trends in citations related to the sub-group

of diseases having a good treatment and the sub-group “needing treatments.” The counts are normalised by the number of all citations in a given year to avoid any biases in the trends caused by the introduction of new journals over time. The estimated

Table 4: Frequency of Citations to Disease Groups in the Biomedical Literature

Year	Diseases with Treatments		Diseases Needing Treatments		Malaria	
	Drug/Vaccine (Per Cent)	All	Drug/Vaccine (Per Cent)	All	Drug/Vaccine (Per Cent)	All
1980	24.0	2,712	18.2	987	22.2	427
1981	26.0	2,924	19.4	1,099	25.1	494
1982	26.0	3,063	21.1	1,322	28.8	638
1983	26.4	3,253	20.0	1,455	26.4	652
1984	27.9	3,266	20.1	1,540	26.7	735
1985	26.9	3,398	20.9	1,673	29.0	758
1986	26.3	3,529	18.8	1,736	24.6	765
1987	25.5	3,564	19.6	1,946	28.1	872
1988	25.4	3,686	22.7	2,034	30.0	919
1989	25.2	4,047	21.3	2,097	30.0	954
1990	25.5	4,129	23.6	2,211	31.6	1,066
1991	26.8	4,229	21.6	2,460	30.3	1,169
1992	26.8	4,321	23.0	2,449	30.4	1,204
1993	27.7	4,117	21.1	2,540	26.4	1,184
1994	26.9	4,348	21.9	2,701	28.6	1,274
1995	28.1	4,345	23.0	2,566	29.8	1,166
1996	29.3	4,106	22.8	2,609	30.8	1,220
1997	29.8	4,298	22.8	2,747	30.0	1,388
1998	29.3	4,226	22.4	2,894	28.7	1,388
1999	31.3	4,169	23.2	3,198	28.8	1,549
2000	31.6	4,166	23.6	3,281	29.6	1,610
2001	34.3	4,053	24.9	3,437	31.4	1,635
2002	32.2	3,875	25.2	3,696	31.0	1,806
2003	33.8	4,112	25.7	3,950	31.5	1,907
2004	32.0	3,786	23.3	3,705	29.0	1,891

Notes: (i) “Diseases with treatments” are Onchocerciasis, Schistosomiasis, Tetanus, Trachoma, Trichuriasis, Ancylostomiasis, Measles, Polio, Syphilis, Leprosy, Pertusis, and Ascariasis.
 (ii) “Diseases needing treatment” are: Malaria, Chagas, Dengue, Japanese Encephalitis, Lymphatic filariasis, Trypanosomiasis, and Leishmaniasis.
 (iii) “Drug/vaccine” is per cent of citations to the group in the online PubMed database with “drug therapy” or “vaccine” in addition to the disease search words.

percentages shown in the figure for each year are quite precise because of the large number of citations.

There is a very clear difference across the two disease sub-groups. The share of biomedical citations to diseases that have good treatments has declined steadily since the early 1990s. By contrast, there has been a steady increase in the share of citation related to diseases “needing treatments” over the entire period beginning in 1980. We do not see in the biomedical literature any rapid acceleration in citation to this group at the end of the 1990s. In fact, if anything the rate of increase appears to have slowed in the more recent years.

The next four panels in Figure 1 indicate the relative importance of different diseases within the group of those “needing treatments.” There are clearly differences across specific diseases. Both Chagas and leishmaniasis have retained a constant share of the citation among the diseases needing treatments – thus having trend patterns similar to the group as a whole. Research related to malaria and dengue, however, appears to be growing relatively rapidly.

Although one might expect that an increase in the potential profitability of drugs for tropical diseases would lead to more research in the science base associated with those diseases, the more direct effect might be a shift within those categories towards more applied research on products - either drug therapies or vaccines. Thus, Table 4 gives the percentage of the citations to each of the two disease sub-groups, and to malaria, which also mention these product types. Both sub-groups show an increase in the share of biomedical activity related to drug products over the 1980-2004 period. The share of product citations among all citations related to diseases “with treatments” grew from 24 to 32 per cent, while for the group “needing treatments” the share increased from 18 to 23 per cent. Product citations became somewhat more frequent in the malaria literature. Some of this growth, however, happened in the early 1980s and there is no clear evidence of any pick up in the trend towards greater product citation in more recent years.

Worldwide Patenting of Therapeutics for Tropical Diseases

Patent applications serve as a useful indicator of early stage research in pharmaceuticals. Innovative activity in this industry is conventionally divided into two phases: “discovery” wherein new candidate molecules are identified, and “development” wherein the chemistry of promising candidates is refined, and drug candidates are put through clinical trials and regulatory testing. Competitive pressures and novelty requirements in patent law lead pharmaceutical companies to patent promptly and prolifically, making patent applications a good measure of inventive activity in the discovery phase. Like the biomedical citations, therefore, we expect trends in patent applications for compounds to treat tropical diseases to provide an early indicator of increased research activity in these areas. To the extent that induced research is directed at technologies with a wider application beyond tropical medicine, counts of patents on therapeutics for tropical diseases are likely to understate the level of R&D activity induced by the TRIPS agreement.

One major problem with using patent data for this purpose is that it can be very difficult to consistently identify the disease to which the invention is applicable. The classification schemes applied by the US patent office (USPTO) and other patent-granting bodies are oriented largely towards chemical structure, and are

relatively unhelpful for identifying narrow disease-specific applications. Our primary method for identifying patent applications relevant to a particular disease was, therefore, searching the text of both patent abstracts and patent claims for keywords. For example, for malaria-related inventions we searched for the words: malaria, malarial, antimalarial, plasmodium, falciparum vivax, ovale. We limited the search by including only patents assigned to International Patent Classification categories A61K or AO1N, which cover pharmaceuticals and pesticides.

A second issue is international coverage. The tables and figures presented below give trends in patenting in the US. In principle one can search in other country patent databases using common keywords to add to the US patent counts. However, it is very difficult to identify which patents in different countries represent new innovations not patented in the US and which are patents covering the same innovations (in the same “family”) which would be duplicates for our purpose. The one private database vendor that had the appropriate international coding of patent families and detailed technology class information to do this exercise properly recently suspended the service.

This is probably not an important concern, however. Most innovations for tropical diseases are likely to be patented in the US, even though it may not be the biggest market for a particular drug. This is because, in relative terms, the military and travellers’ markets in developed countries are likely to be a relatively significant source of potential revenue and therefore worth protecting. Most importantly, trends over time in the patterns of patenting should not be affected by the limitation in coverage.

Table 5 gives the results of compiling counts of US patents using keyword search criteria. Counts are by the date of application, which places the timing of the invention quite close to the research activity which generates it. The first three columns in Table 5 give counts of patents related to the group of diseases

Table 5: Frequency of US Patents Granted by Disease Groups

Year	Diseases with Treatments			Diseases Needing Treatment			
	Schistosomiasis	Trachoma	Of which: Malaria	Leishmaniasis	Chagas	Dengue	Of which: Japanese Encephalitis
1980	10	3	0	10	7	2	0
1981	12	2	0	13	8	2	1
1982	19	6	0	11	7	0	2
1983	10	3	0	12	10	1	1
1984	17	0	0	12	10	2	0
1985	29	4	0	13	10	1	0
1986	25	1	0	7	5	1	0
1987	20	1	0	17	14	2	0
1988	18	2	1	13	11	2	1
1989	29	1	1	22	20	2	1
1990	15	0	0	21	19	2	3
1991	13	2	0	27	21	3	4
1992	26	2	0	23	18	1	2
1993	46	3	0	31	27	3	2
1994	66	1	0	60	44	15	7
1995	169	6	0	103	75	17	10
1996	62	2	0	59	43	17	1
1997	79	5	2	63	49	13	8
1998	67	7	1	66	46	11	3
1999	73	9	3	75	52	20	5
2000	80	4	4	90	66	15	5
2001	46	2	3	55	45	8	5
2002	12	0	0	29	26	4	2

Notes: (i) Year is that of patent application.
(ii) “Diseases with treatments” are Onchocerciasis, Schistosomiasis, Tetanus, Trachoma, Trichuriasis, Ancylostomiasis, Measles, Poliomyelitis, Syphilis, Leprosy, Pertussis, and Ascariasis.
(iii) “Diseases needing treatment” are: Malaria, Chagas, Dengue, Japanese Encephalitis, Lymphatic filariasis, Trypanosomiasis, and Leishmaniasis.

“with treatments” and two of its components, schistosomiasis and trachoma. The next column gives counts of patents related to diseases “needing treatments”. In the final columns we give counts for the component diseases malaria, leishmaniasis, Chagas’ disease and dengue. Some patent applications include search words related to more than one of our target diseases. When this happens, the patent is counted for each disease, but is included only one time in the sub-group total. As a result, disease-level counts can add up to a number greater than the total indicated for the sub-group.

Although the raw numbers give some insight into the relative level of research activity across the diseases, it is important to normalise the series when interpreting their trends. There has been a steep upward trend in the series of overall patenting in pharmaceuticals reflecting the remarkable expansion of the industry over the past three decades and intensification of pharmaceutical research activity. Thus, in Figure 2 we show the trends over time in worldwide patenting related to tropical diseases as percentages of total pharmaceutical patenting.

As in Figure 1, the first two panels in Figure 2 give trends for the two disease sub-groups. The numbers of patents that we are dealing with in all cases are small. Patenting related to tropical diseases is always less than 2 per cent of overall pharmaceutical patenting (where the latter is defined as technology classes A61K and A01N). As a result, the data trends are not very smooth. However, the total number of pharmaceutical patents in each year is large so the percentages are quite precisely estimated. Estimated standard errors are on the order of 0.1 percentage points.

There is clearly a difference between the two sub-groups. For the group of diseases with treatments we see spikes in patenting in 1993 and 1995 (which were not observed in the citations data). This increase in activity was spread across almost all of the included diseases. However, the increase was not sustained and, to the contrary, there has been a falling off in the patenting for this group since the end of the 1990s.

The pattern for the patents related to diseases still needing good treatments is quite different. For this group there has been a persistent and gradual increase in activity since the late 1980s. There is some evidence of an extra uptick in the mid-1990s. However, what is most interesting is the apparently rapid increase in patenting for this group in early 2000s, going from 0.8 to 1.4 per cent of all pharmaceutical patenting in just a few years. It is too early to tell say whether this will be a sustained change in the trend.

The next four panels indicate the relative importance of different diseases within the group of those “needing treatments”. Malaria, for example, is by far the largest target for R&D activity among the included diseases, representing 60 to 90 per cent of all patents in this group. Its share in 2002, the last year of the data, reached the historical high of 90 per cent. It follows that the recent growth in patented innovation related to malaria has been even more rapid than the increase for the group overall. Similarly, in the final panel we see that the share of patents related to dengue also increased markedly in the early 2000s. Patenting related to leishmaniasis and Chagas followed more or less the pattern described for the group. These trends mirror those we saw in the citations data.

Pharmaceutical Patenting by Indian Inventors

As a second patent-based indicator of relevant R&D activity, we have collected information on all pharmaceutical patenting

in the US and at the European Patent Office (EPO) by inventors based in India. Unlike the data just discussed, these patents are not specifically for tropical disease therapies. One rationale for looking at these data is the following. For centuries, Indian inventors have had the ability to patent in the US and in Europe and to profit through sales of patented products in the global market.¹¹ Thus the prospect of new patent-generated profits in developing country markets would present only a small marginal increase in their incentive to invest in R&D directed at global products. Because inventors in developing countries have a comparative advantage in research on tropical diseases, the prospect of patent-based profits in developing country markets might induce a greater than marginal increase in their overall research efforts. Assuming that the more important discoveries would also be patented abroad, we would then expect to see increased pharmaceutical patenting by Indian inventors in the US and in Europe.

Table 6 displays changes over time in pharmaceutical patenting by Indian inventors. Again, a “pharmaceutical” patent is defined as one falling in the International Patent Classification categories A61K or A01N; an “Indian” patent is identified by the country of priority being India or, in the case of US patents, the address of an inventor being India; and the “year” is that in which the application was made.¹² The first column in the table is numbers of US pharmaceutical patents granted to Indians and column 2 gives these relative to all patenting by inventors based in India. The third column gives the number of applications made for pharmaceutical patents at the EPO by Indian inventors. This is compared to all pharmaceutical applications received by the EPO in column four. Because of lags in application and granting, there is truncation in the last numbers of the series so the percentages are more informative.

The numbers of patents presented in Table 6 are small but increasing. Pharmaceutical research by Indians has remained a fairly constant share of all research activity undertaken by Indian patentees. Pharmaceutical innovations accounted for about 25 per cent of all US patents to Indian inventors over the 1990s to 2002, although this is up from 15 per cent in the 1980s.

Table 6: Trends in Pharmaceutical Patenting by Indian Inventors

Year	US Patent Grants			EPO Patent Applications		
	Number	All Indian (Per Cent)	All Pharma (Per Cent)	Number	All Indian (Per Cent)	All Pharma (Per Cent)
1980-84	12	14.5	0.09	1	100	0.00
1985-89	23	16.9	0.13	0	0	0.00
1990	11	28.2	0.26	1	0	0.01
1991	14	36.8	0.37	4	100	0.06
1992	18	36.7	0.39	1	50	0.01
1993	11	16.7	0.21	1	0	0.02
1994	9	12.9	0.13	1	50	0.01
1995	17	19.5	0.17	3	100	0.04
1996	24	19.7	0.38	3	100	0.04
1997	40	23.0	0.52	3	33	0.03
1998	44	21.7	0.59	9	50	0.09
1999	43	15.9	0.54	23	43	0.23
2000	70	23.3	0.95	35	55	0.33
2001	63	19.8	1.20	36	47	0.36
2002	40	25.0	2.20	16	27	0.31

Notes: (i) Pharmaceutical patents are those in International Patent Classification groups A61k or A01n.

(ii) “Indian Patents” are those with an inventor with an Indian address or Indian priority in the US patent data, and those with Indian priority in the European patent data.

(iii) US patent counts include those granted as of March 18, 2004; European patents include those applied for as of May 6, 2004.

More significantly, the data suggest that Indian inventors are indeed becoming increasingly important participants in world pharmaceutical innovation. There has been a significant increase in their representation among pharmaceutical patentees, beginning in the mid-1990s and accelerating through 2002. In that year, inventors working in India were the source of over 2 per cent of all US pharmaceutical patent applications. The same trends are apparent in the EPO data, although the numbers there are very small.

Survey of Indian Pharmaceutical Companies

The difficulty with interpreting the total patenting by India-based researchers is that there are other reasons, beyond that suggested, for why their patenting might have increased. The recent business press has been full of stories discussing whether or not multinationals should or will shift more of their R&D to India and other developing countries in an effort to lower research costs, and emphasising the increasing sophistication of in the R&D capabilities of firms based there.¹³

Thus, we have completed the second round of a repeated survey of Indian firms designed to capture more precisely changes that might arise as a result of the new patent laws. Specifically the survey seeks to understand how much of the R&D being done by firms in India is related to developing country markets. The survey results complement the longer trends available in the statistical data sources already discussed.

The two basic questions are: Thinking about your current research projects underway at a pre-clinical stage,

- (1) For how many of them is it the case that more than one-half of sales revenue is expected to come from developing country markets and what annual dollar amount do these projects represent?
- (2) How many of them are directed at one or more of the following diseases (list-Table 1) and what annual dollar amount does this set of projects represent?

These questions capture the two dimensions of demand differences: different priorities regarding the cost/effectiveness trade-off or other characteristics and different disease patterns. We have surveyed the largest pharmaceutical firms operating in India, both Indian-owned firms and multinational subsidiaries. The population of firms includes all members of the Organisation of Pharmaceutical Producers of India (OPPI), the Indian Pharmaceutical Association (IPA) and non-members also active in R&D. In total, the survey was sent to 65 CEOs or managing directors.

In addition to the questions above, the survey instrument includes further questions regarding development research [see Lanjouw and MacLeod 2005, for the survey instrument]. The reason for including these questions even though one would expect patent protection to be a more important stimulus to innovative research is twofold. First, we would not expect most growth in new therapies coming from this quarter. From discussions in the mid-1990s with many firms based in India it was clear that, faced with the introduction of patent protection, only a small number planned large increases in spending on discovery research directed at novel compounds. The substantial investment in personnel and infrastructure required to build up a discovery R&D capacity was prohibitive for most. This has been borne out by events. Of those that have followed the strategy of turning to discovery research, the targeted markets are large and global: cancer, diabetes, and so on. On the other hand,

subcontracted development work – both by multinational subsidiaries for their home offices and by India firms for non-affiliates – is undertaken by a much larger group of firms and is of growing importance. Since a western firm with a new potential drug therapy appropriate to a developing country market might well consider engaging an Indian firm to work on its development, repeated surveys should not only track research within India but should also pick up changes in activity by western firms in this area.

The first round of the survey was fielded in 1998, with results summarised in Lanjouw and Cockburn (2001). In that round 20 questionnaires were completed, of which five were multinational subsidiaries. The total R&D expenditure of the firms together was 43 million 1998 dollars, which was about 90 per cent of all R&D investment in India in that year. Of the responding firms, nine reported that they did not have any research or development projects on tropical diseases or targeted at developing country markets. The 11 who did report having such projects allocated 6.9 million dollars to them. Thus, about 16 per cent of R&D expenditure among the 20 respondents was directed towards the specified types of projects. As expected, only 1.3 million dollars or 19.7 per cent, of that expenditure was discovery research as opposed to development research.

Almost half of the relevant R&D was for products targeted at developing country markets but not for diseases on the list of Table 1 (that is, products for diseases found globally but having characteristics suited to the LDC environment). It is this part of the stimulus to innovation created by patent protection in the developing countries which would be missed by only tracking changes in research on tropical disease therapies. Since the latter is all that is possible using standard statistical data sources, the fact that almost half of Indian research is of this second type demonstrates the importance of trying to create a series of survey data to complement the statistical databases.

The second round of the survey was completed by 31 firms, of which seven were multinational subsidiaries. Thirteen of the respondents indicated that they did not perform any R&D within India. However, with \$207 million 2003 dollars of R&D spending in 2003-04, the remaining 18 respondents together were the home of almost all of the corporate pharmaceutical research in India in that year. (Just two major firms declined to participate.) Of the 18 respondents performing R&D in that year, 14 firms, or over three-quarters, indicated that they did not have any research projects targeting developing country markets nor the diseases concentrated there. Of those that did have such projects, they together allocated no more than 21 million dollars to this category.¹⁴ This amount is at most 10 per cent of all R&D investment for the group of respondents, and thus well below the 16 per cent found for the earlier baseline survey. As in the earlier survey, about a one-third of the targeted R&D is indicated as “discovery” R&D and the rest “development”, and a significant part appears to be for products treating global diseases but designed specifically for marketing in developing countries.


IV Concluding Comments

Taken as a whole, the various data sources examined in this paper point to a steady increase in pharmaceutical inventive activity in some areas of specific interest to developing countries. There are a number of difficulties with interpreting these data,

in particular with establishing the precise timing of activity, and in some instances the time series may be too short to draw meaningful conclusions about trends. Nonetheless some interesting provisional conclusions can be drawn.

The level of innovative activity related to diseases specific to poor countries remains extremely low relative to pharmaceutical research overall. Among this targeted group of diseases, the subset already having good treatments available has continued to see a persistent downward trend in its share of US pharmaceutical patenting and biomedical citation over the past 20 years. By contrast, the set of diseases still in need of better low-cost treatments has seen a trend increase in its share of patenting and bibliometric citation, normalised by the relevant (growing) population totals. In the case of patenting, we observe in the data what may be the beginning of a speeding up of this trend increase in the early 2000s, but it is too early to be confident that it will persist. If it does persist, it could be interpreted as a response to the expansion of patent rights and consistent with market considerations influencing the allocation of pharmaceutical research effort. On the other hand, we do not see any trend increase in the biomedical citations series late in the period for the same disease group (although a growing share of these citations appear to be related to products vs basic science). Further, given that malaria has been the particular focus of a variety of public sector and public/private initiatives in recent years, it would be hard to claim with any confidence that new patent rights were driving any persistent surge in research on that disease.

The data on patenting by Indian inventors in the US and Europe, together with insights from interviews with Indian executives and the two firm surveys, are again suggestive, rather than conclusive, but do raise some interesting issues. Most notably, it is clear that the impact of the TRIPS agreement on incentives for the research-intensive companies based in the OECD is only part of the picture: strengthened IP rights may also be stimulating domestic R&D in countries which have not previously emphasised them. The data on patenting in the US and the European Union shows that inventors based in India are increasingly players in the world of pharmaceutical R&D, now taking out over 2 per cent of all pharmaceutical patents in the US and a smaller but rapidly growing share in Europe.

One might expect, and it has been suggested, that researchers working in India would focus on products relevant to their own markets where they might be thought to have a comparative advantage. Company executives made plain the contrary in interviews conducted in the mid-1990s: any discovery research, they said, would be on global diseases and on products for the worldwide market. Interestingly, the baseline survey results for 1997-98 suggested that, while this may have been true looking forward, Indian firms were nonetheless allocating a significant portion of their R&D budgets to tropical disease research and products tailored for developing country markets. With the second round survey for 2003-04, we see that while overall investment in pharmaceutical R&D in India has surged over the past five years, it has become less targeted towards the health needs of the developing world. A natural explanation for this would be that the incentives created by local patents are more than offset by the push towards global products created by growing numbers of research relationships with multinational firms. 

Email: lanjouw@are.berkeley.edu

Notes

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- 1 TRIPS is the commonly used acronym for the Agreement on Trade-Related Aspects of Intellectual Property Rights (Annex 1C of the Agreement Establishing the World Trade Organisation).
- 2 This point was taken up and formalised in a theoretical model by Diwan and Rodrik (1991).
- 3 Compulsory licences are issued by the government and allow another firm to manufacture or sell a patented product without the agreement of the patent holder.
- 4 See, for example, Harvey Bale, head of the International Federation of Pharmaceutical Manufacturers in *The Guardian Weekly*, February 18, 2003, at <http://www.guardian.co.uk/aids/story/0,7369,897340,00.html>; and Raymond Gilmartin, CEO, Merck, IFPMA Presidential Address, available at <http://www.merck.com/newsroom/executivespeeches/100202.html>.
- 5 In order to make meaningful comparisons over time, these figures do not include special large programmes related to bioterrorism. NIH programmes for smallpox and anthrax were budgeted at \$375 million for 2004 and these are likely to grow.
- 6 For announcement see <http://www.whitehouse.gov/bioshield>.
- 7 Cooperative Research and Development Agreements (CRADAs) and related contracts were created in the mid-1980s to encourage joint public/private research efforts.
- 8 Available online at <http://grants.nih.gov/grants/award/state/state.htm>
- 9 This is a service of the National Library of Medicine. Further information can be found at <http://www.nlm.nih.gov>.
- 10 In doing this we were advised by Gerald Keusch, associate dean for global health at the Boston University School of Public Health and formerly director of the Fogarty International Centre at the NIH. The breakdown is done to see if there are broad differences in patterns in the data and is not intended to have a precise interpretation. The grouping of diseases is also not redone for each year going backwards in time, so it may be a less meaningful breakdown of the data for 1980 than in 2002.
- 11 Due to the principle of "national treatment" enshrined in the Paris Convention Treaty of 1883.
- 12 The country of priority is the first country in which a patent application is made on a given innovation. Typically this is the country in which the research was done.
- 13 See, for example, "Novartis Research Centre: It's a Toss-up between India, China," available at <http://www.thehindubusinessline.com/2004/11/24/stories/2004112403560100.htm>.
- 14 One unclear response precludes our giving a specific figure.

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