COMMENT

How TRIPS benefits Indian industry and how it may not benefit the Indian people

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The accession to TRIPS post-2005 is a milestone in the history of India's pharmaceutical industry whichever way you look at it. Easy access, through reverse engineering, to innovator drugs marketed abroad has been stopped. Indian industry, if it still wants to make drugs under international patents, has to buy technologies for those new innovator drugs if they are on sale; enter into exclusive marketing/voluntary license arrangements, or apply for a compulsory license (CL) and hope that it is granted. The last is unlikely because the government of India, the agency to issue CLs, is wary of being seen as unfriendly to multinational corporations (MNCs) and the principal western governments where these MNCs are located - unlike the Thai government which issued CLs for four anti-cancer drugs (1).

So have the bottom lines of Indian drug companies been hit after Jan 2005? On the contrary, the evidence is that the Indian pharmaceutical industry has never had it so good. Sales are booming even as there has been a move to shake out small players through government regulations like Schedule M that require upgradation of manufacturing facilities at great expense. The medium players are becoming big and the big ones are becoming bigger. Apart from increased overpricing of older, well accepted drugs, acquisitions (including foreign acquisitions) and mergers (after a fashion) are one reason for this boom; exports are another reason and the expanding domestic market a third. A fourth and most relevant reason is that many top-selling useful drugs are either out of patent or getting to be out of patent.

But can Indian industry innovate? Can it develop block buster drugs? To answer this, we must examine certain questions.

What is the record of innovation in the drug industry the world over?

There is enough evidence to indicate that drug development is becoming tougher even in countries with a record of such drug development. A recent editorial in *Nature Reviews Drug Discovery* notes:

> Each year for the past 5 years, *Nature Reviews Drug Discovery* has featured an article discussing drug approvals over the previous year, and 2008 is no different ... Regrettably, the 'scorecard' of novel drug approvals this year also tells a familiar story; indeed, the total of 17 new molecular entities (NMEs) and 2 biologic license applications approved by the US FDA makes 2007 the worst year for novel drugs assessed in these terms for a quarter of a century.
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> ... Is over-cautious regulation to blame? Is there a shortfall in the number or quality of submissions being made to the regulators? And are the scientific challenges inherent in the novel therapeutic strategies now being pursued greater than those in the past?
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> In some cases, the answer might be all of the above. A potential example could be provided by one of 2007's high-profile investigational therapies not to be approved: the prostate cancer vaccine Provenge (Sipuleucel-T; Dendreon). Certainly, the science behind Provenge is novel: if it had been granted approval by the FDA, it would have been the first cancer vaccine of any kind to be introduced in the US.
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> However, perhaps owing in part to uncertainty over the most appropriate way to evaluate such a novel therapy, Provenge failed to meet its primary end point of increasing time to disease progression in the pivotal clinical trials. Nevertheless, although the trials had not been designed to show this, subsequent analyses indicated that Provenge extended median overall survival. On the basis of these results, an FDA advisory committee voted in favour of its safety and efficacy.
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> The subsequent - and unusual - decision by the FDA to overrule the advisory committee's decision and delay approval, asking for further data, has generated considerable controversy, in part because of alleged irregularities in the decision-making process. Even putting aside such potential irregularities though, the decision might be taken to indicate growing regulatory caution. This caution could be even stronger for highly novel therapies, such as cancer vaccines, that the regulators are unfamiliar with. (2)

Are stricter intellectual property regimes conducive to innovation?

Drug development literally involves standing on the shoulders of not only giants but also on the many not so dramatic discoveries of others. Not sharing data, strict data exclusivity and data protection regimes as are being demanded by strong IP regime protagonists discourage innovation. It is pointed out that:

> ... if patents were the source of medical innovation as claimed by intellectual monopoly apologists, the large historical and cross country variations in the patent protection of medical products should have had a dramatic impact on the pharmaceutical industries of the different countries. In particular, at least between 1850 and 1980, most drugs and medical products should have been invented and produced in the United States and the United Kingdom, and very little if anything in continental Europe. Further, countries such as Italy, Switzerland and, to a lesser extent, Germany, should have been the poor sick laggards of the pharmaceutical industry until the other day. Instead, as everyone knows since high school, the big time opposite is and has been true. This is as macroscopic a contradiction of the intellectual monopoly apologists' argument for patents in general, and for medical patents in particular, as one can possibly imagine. (3)

Apart from that if one has to constantly look over one's shoulders to see what patent one is violating when doing drug discovery, it in effect leads to patent gridlock - a situation in which even big drug companies are unable to do potentially life-saving research because they cannot negotiate the rights to all the patents necessary for the research (4).

Does Indian industry have the infrastructure and money?

Most research and development leading to the innovations and blockbuster drugs had their origins in publicly-funded institutions even as drug companies reap the profits The ordinary public, as Marcia Angell points out in *The truth about drug companies* (5), ends up paying twice: once for the research through taxes and again for buying the medicines at high prices through insurance or out of pocket payments.

Some examples of publicly funded blockbusters: Taxol, an anti-cancer drug, was supported by the National Institutes of Health (NIH). Drugs like Gleevec, Epoeitin, Zidovudine were discovered in public-funded university departments (6). And from 1998 to 2002, of 415 US FDA applications, only 14 per cent were innovations; the rest were me-too drugs. And as far as research and development relevant to tropical countries, only 13 out of 1,223 new chemical entities discovered between 1975 and 1997 were for tropical diseases

According to testimony to the United States Senate on federally funded pharmaceutical inventions in that country (7),

> Of the 37 cancer drugs developed since 1955, the federal government was directly or significantly involved in the preclinical development of 18, and played some role the preclinical research for 10 others. In only 9 cases was NCI not involved at all in the preclinical research. When the drugs reached the stage for clinical research, NCI's role was even more pronounced. NCI played an important role in the funding of clinical research for 34 of the 37 drugs, or 92 percent of the entire group.

The pharmaceutical industry states that it costs around US $800 million - Rs 3,200 crore or Rs 32 billion -- to develop a single drug. There have been valid criticisms of the $ 800 million figure being an highly inflated estimate (8, 9, 10, 11, 12). Assuming that these estimates are inflated and the actual cost is US$ 200 million - Rs 200 crore (Rs 2 billion) using purchase power parity rate of Rs 10 per dollar -- we may convince ourselves it is in the realms of possibility for India to develop new drugs.

But there is a tremendous shortage of skilled human power today in India in every sector. Even in the information technology (IT) sector "only 8-10 per cent of our 495,000 engineers graduating annually are qualified to work in this sunrise industry." (13) And it is the "smarter" young people who go to IT and management. Science education today is in its nadir since independence. The number of young people opting for basic science research as a career is dwindling even as our universities are in shambles. With a nosedive in both the quality of science and the numbers of people viewing it as a career, it is too much to expect quality research output in solar energy let alone in drug discovery. At best, seeing the rush to biotech related degrees and jobs, one may hope for some discoveries there. But, then, how much are we investing in research?

The latest available figures show that we have about 116,000 people in India engaged in scientific research and development (R&D) activity. By contrast, the US has 1.3 million people in R&D, despite its total population of 290 million being less than a third of our one billion. Per capita, its R&D manpower is 40 times larger than ours - a personnel of 4,500 per million, as compared to our 110 per million. If you include all US workers who need a BSc level knowledge of science and engineering, the S&T workforce in the US is even larger - about 9.2 million(14).

Let us look at some of the figures invested in research for new chemical enitities: Dr Reddy's (Rs 80-100 crore annually); Ranbaxy's (around $100 million in 2007); Nicholas Piramal: $ 80-90 million (so far including a R & D centre and infrastructure); Glenmark ($25-30 million in eight years); Biocon (Rs 100 crore so far); Advinus (Rs 200 crore so far); Wockhardt (Rs 200 crore so far) and Lupin (Rs 100 crore since 2001)(15). These figures are impressive by Indian standards. But the US NIH alone spent $23 billion (twice the sales of the entire Indian drug industry) in 2004. And a look at the 2004 R & D figures for 10 MNCs (box) shows how much they spend on research. The annual R&D expenditure of Sanofis alone is about the same as the sales of the entire Indian drug industry.

The point is that India's pharmaceutical industry does not have history or economics on its side; nor does it have the intellectual backup of a sound university system and cutting edge R & D institutes of an industrialised country.

Research for whom?

But in any case, we must remember that business, trade and discovery are for human development, and not the other way around. Unfortunately the TRIPS/WTO thinking endorses the latter. One result is that corporate investments will go for

diseases of the affluent rather than diseases afflicting the poor where there is less scope for enormous profits.

This is all the more reason why India needs different strategies for supporting R&D for diseases of importance to its poor as well as diseases affecting the poor in all countries. A new paradigm for funding and doing research for public purposes is required (15). It cannot be stressed enough that many of the developing countries in the vanguard of advocacy for IP rights themselves had IP protection in pharmaceuticals only after arriving at a certain stage of development. Now that they have arrived, they seek to close the gates.

Even without patents, 15 per cent of the world's population consumes 91 per cent of the world's production of pharmaceuticals (16). Industrialised countries currently hold 97 per cent of all patents worldwide, while 80 per cent of patents granted in developing countries belong to residents of industrial countries.

What sort of rights does IP protection confer? According to the Report of the Commission on Intellectual Property Rights (17),

> The conferring of IP rights is an instrument of public policy, which should be designed so that the benefit to society (for instance through the invention of a new drug or technology) outweighs the cost to society (for instance, the higher cost of a drug and the costs of administering the IP system). But the IP right is a private one, so the financial benefits and costs fall on different groups within society. The IP right is best viewed as one of the means by which nations and societies can help to promote the fulfilment of human economic and social rights. In particular, there are no circumstances in which the most fundamental human rights should be subordinated to the requirements of IP protection. IP rights are granted by states for limited times (at least in the case of patents and copyrights) whereas human rights are inalienable and universal. For the most part IP rights are nowadays generally treated as economic and commercial rights, as is the case in TRIPS, and are more often held by companies rather than individual inventors. But describing them as "rights" should not be allowed to conceal the very real dilemmas raised by their application in developing countries, where the extra costs they impose may be at the expense of the necessities of life for poor people.

So if I were a big Indian drug company, I would invest in R & D even if it were small by western standards; focus on the generics sector as the patents of several useful innovator drugs come off the market; build my brand equity on generics internationally; get the government of India to jointly sponsor industry-wide efforts on drugs for relevant diseases for India; go big on acquisitions internationally till I get one company with a considerable R & D clout; and then hope for a breakthrough to ride on. Or serendipity.

If I were a hapless citizen of India, I would hope for the TRIPS system in WTO to collapse; and for the development of some alternative form of rewarding innovations in medicines that matter to me and my family and my community.

R&D Expense Level in Leading Pharma Companies in 2004

Sr. No.	Company	R & D Spend in 2004 (in billions)	% of Sales
1	Sanofi-Aventies	$9.3	29.2%
2	Pfizer	$7.5	16.3%
3	Roche	$5.4	31.2%
4	Johnson & Johnson	$5.2	23.5%
5	Glaxo SmithKline	$5.2	16.6%
6	Merck	$4.0	18.6%
7	AstraZeneca	$3.8	17.8%
8	Novartis	$3.5	18.9%
9	Bristol-Myers Squibb	$2.5	16.1%
10	Wyeth	$2.5	17.9%
Total Top 10 Companies		$48.9	23.8%

Source: Pharmaceutical Executive in May 2005 (IMS Health data)

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