Impact of India’s New Patents Law 2005: A Physician’s Perspective

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Independent India since 1947 had extensive and ultimately unsuccessful discussions with multinational drug companies (MNCs) for the production of essential modern drugs in India by paying royalties for the right of manufacture and transfer of technology. The Soviet Union gave the fermentation technology to make penicillin in India. But MNCs fought tooth and nail and wanted Indian drug patent laws to resemble those in other countries. It was Yousuf Hameid who persuaded the then Indian Prime Minister Indira Gandhi in 1970 to modify India’s old 1911 patent laws so that only process patents (not product patent) were recognized. After 1972 it became possible to produce and sell in India drugs still under patent protection in other countries, as long as these drugs were manufactured through unique processes. This policy has served India extremely well, as evidenced by the fact that today drug prices in India are among the lowest in the world. India is not only self-reliant in drugs but it exports quality drugs at low cost to 200 Asian and African countries. Forty percent of India’s drug manufacture is exported.

WTO & TRIPS: The World Trade Organization (WTO) was formed in 1995. It established minimum standards for a set of Intellectual Property Rights (IPRs) that WTO members have to institute through national legislation. The Trade-related Intellectual Property Rights Agreements (TRIPS) has become the most contentious agreement of the WTO. IPR is not a trade issue, and WTO is about mutually gainful trade. TRIPS was placed in the WTO because the developed countries wished to make use of its effective dispute settlement system in order to ensure enforcement of their discipline on developing countries. IPRs are not natural rights, but rather privileges granted to inventors to reward their inventions and to enable recovery of cost. The TRIPS agreement has resulted in a very significant shift in the balance in the IPR regime towards monopolistic privileges of IPR holders, away from public interests, especially in developing countries where there is potential for maximum damage to the poor. Since year 2000 many NGOs world-wide are clamouring for the removal of TRIPS from WTO.

Patent Amendments in India after TRIPS: Before the creation of WTO, individual countries were free to have their own Patent Laws. TRIPS came into force on 1st January 1995. For countries like India who did not grant product patents in pharmaceuticals, TRIPS provided a three stage frame.

1. Introduction of a facility (“mail box”) from 1st January 1995, to receive and hold product patent applications in the field of pharmaceuticals (and agricultural chemicals). Such applications will not be processed for the grant of product patent till the end of year 2004. But exclusive marketing rights (EMR) can be granted for the applicant if a patent has been granted in some other WTO member country and the application has not been rejected in the country as not being an invention.

2. From 1st January 2000, compliance with other obligation of TRIPS viz. rights of product patentee, term of patent protection, compulsory licensing, reversal of burden of proof etc.

3. From 1st January 2005, introduction of full product patent in all fields including pharmaceuticals. All the product patent applications in the “mail box” (since 1995) are required to be taken up for examination from 1st January 2005 (over 7000 such applications are awaiting disposal in India today by Patent Examiners).

India’s compliance of TRIPS requirements (under constant pressure from USA and European Union) was forced by WTO with a deadline of April 1999. Hence an ordinance was promulgated followed by an Act passed in March 1999 which amended the 1970 Patent Act with retrospective effect from January 1995, to implement mail box facility and Exclusive Marketing Rights (EMR).

Another Act, The Patents (Amendment) Act 2002 made 64 amendments of the Patent’s Act 1970 relating to the term of patent (20 years), exclusions to compulsory licensing and so on.

A third amendment was required by the end of 2004 to replace the EMR system and to introduce product

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AIDS patients at a cost of US $ 350 per year compared to stavudine + lamivudine + nevirapine, to the African available a combination of 3 anti-retroviral drugs – Hameid of CIPLA (India) made history by making Pharmacotherapy) drugs : the drug. be used to prevent generic companies from producing obtained after 1995 for a drug patented before 1995 can point of contention is whether a secondary patent imatinib mesylate. Further, the patent in India will expire Indian companies from manufacturing and marketing which has passed an interim order restraining six Natco has challenged the grant of EMR to Novartis in crystal form) and got a patent and marketing approval in Australia during 2001-2003. In November 2003 modified the crystal form of imatinib mesylate (beta for the Novartis product, generic Indian version cost this drug. Compared to the price of Rs. 120,000 per month A number of Indian companies (Natco, Ranbaxy, Sun Pharma, Cipla, Emcure, Intas, Hetero) have been manufacturing and marketing generic versions of this drug. Compared to the price of Rs. 120,000 per month for the Novartis product, generic Indian version cost between 9000 and 12000. Then in 2001 Novartis in New York Times editorial condemned the obnoxious clauses in the Patent ordinance that would harm the poor. Obtaining compulsory licence has been deliberately made very slow & difficult. Retired Supreme Court Judge Krishna Iyer in a letter to the Prime Minister has pointed out “the failure to ensure essential safeguards in the key areas of public health, which would clearly demonstrate the power of influence and the reach of MNCs to the corridors of power”. The WHO Geneva has written to the Indian Health Minister that after the WTO / TRIPS acceptance, India should ensure necessary steps to continue to cater to the needs of the poorest countries of the world. Mr. B. K. Keayla, convener, National Working Group on Patent laws has criticized the Patent (Amendment) Act 2005 for ignoring TRIPS flexibilities and freedoms and Doha Declaration and options available, to suit the powerful MNCs. Lessons from Gleevec™ : Novartis had a patent granted in USA before 1995 for the new chemical entity imatinib mesylate. A number of Indian companies (Natco, Ranbaxy, Sun Pharma, Cipla, Emcure, Intas, Hetero) have been modifying the drug? Will these become unavailable with great detriment to the patients? The Bill 2003 did not address this important issue and the ordinance of 2004 has only partially dealt with it. The important question is: if and when a product patent is granted to any mailbox application what will happen to the generic companies which are currently producing the drug? What needs to be done now? 1. “Mail Box”: Scrutiny for product patent applications should be open and transparent. All the 7000 claims should be subjected to pre-grant opposition (an important provision in the 1970 Patent Act). TRIPS does not oppose this provision. 2. Prior use exception: It is important to safeguard the continued production in India of the drugs produced between 1995 and 2004. Such exceptions
are held valid under Article 30 and compatible with TRIPS. There should be no vagueness about this issue, which according to critics has been deliberately introduced to suit MNCs.

3. **Present evergreening of patents**: The National Institute of Health Care Management Research (NIHCM) USA 2002 report: “Changing Patterns of Pharmaceutical Inventions: New Patents,” has observed that drug manufacturers patent a wide range of inventions connected with incremental modifications of their products including minor features such as inert ingredients and the form, colour and scoring of the tablets. All these tactics are designed to discourage generic drug manufacturers from developing a competitive product. We should ensure that such frivolous patents are not entertained in India. TRIPS does not require the granting of additional patents for new uses or new dosage forms of known drugs.

4. **Compulsory licensing**: For the production of important and life-saving drugs. This provision is 100% compatible with TRIPS article 31(b). Member countries have the right to grant compulsory licences and freedom to determine the grounds there of. Every provision of TRIPS should be read in the light of its Article 7 objectives and Article-8 principles.

Taking the example of drugs for HIV / AIDS, the poor people should not have to wait for 20 years till the MNCs have recovered their investment in research and development of these drugs. One practical suggestion is to pay the patent holder a 4% royalty on sale by the Indian drug manufacturer who will produce the drug under compulsory licence. Paying for rights as a percentage of sales would distribute research costs more equitably and realistically. Compulsory licensing should cover all diseases of national importance – Malaria, Kala Azar, Tuberculosis, HIV, Viral Encephalitis, Cancer, Hypertension, Diabetes, Atherosclerosis etc. It is very important to specify a definite time period – one to three months – for this process of compulsory licensing which must be simplified and streamlined. Unfortunately this issue has been ignored. Today the process is very time-consuming and cumbersome. Knowing the state of our politics and bureaucracy, any vagueness in the process of compulsory licensing will be an excuse for inaction for the inept and a source of income for the corrupt.

**300 Essential Drugs and Generic Drug Companies**: In an address to the WHO in 1981, Prime Minister Smt. Indira Gandhi had said that “No one will be allowed to make profit out of illness and misery of the poor people in India”. Considering that more than 80% of illness related expenditure including drugs comes out of the private Indian pockets – rich as well as poor, affordability of essential drugs is a crucial issue especially for the poor. In 2002, under the leadership of Prof. Ranjeet Roy Choudhary, the Delhi Society for Promotion of Rational Use of Drugs, in collaboration with WHO – India programme on Essential Drugs, published Standard Treatment Guidelines. These are specifically mentioned in India’s National Health Policy document. The 300 essential drugs mentioned in the Guidelines, will need periodic review with additions and deletions (such as nimesulide withdrawn from the market recently).

The challenge before generic drug manufacturers is to make these 300 essential drugs available to the poor at a price they can afford. A glaring example is iron supplement urgently needed for 600 million Indians (especially women and growing children). At one time Glaxo’s ferox sulfate (Fersolate) at 5 paisa per tablet was the most valuable drug for the poor, but its manufacture was stopped due to non-profitability. Today out of 200 formulations containing iron in various forms (sulphate, fumarate, gluconate, ammonium citrate, carbonyl, polysucrose etc) only four cost less than one rupee a day. 60 brands of iron poly maltose costing over 2-3- rupees a day are sold although they have been shown to be ineffective (BC Mehta 2003). The prototype of Glaxo’s fersolate should be the goal of generic drug companies to provide the 300 essential drugs for the poor Indians. Government should help the drug companies in a pro-active way to achieve this goal. Drug companies should not be blamed for the current health plight of the poor which has resulted from grossly insufficient budgetary provisions, lack of political will to firmly implement policies and plans, coupled with administrative incompetence and corruption.

**Making drugs, not profits**: The business model embraced by pharmaceutical and biotechnology industries will never meet the needs of the 4 billion poor in the world for essential drugs at affordable prices. In the year 2000 a dynamic duo Ahvie Herskiwitz and his wife Victoria Halo took the novel step of starting a not-for-profit drug company One World Health, with virtually no resources except human capital. Phillips Desjeux of WHO Geneva suggested to them that an opportunity existed for an off-patent antibiotic paramomycin that needed one last clinical trial to prove its worth in treating leishmaniasis (Kala Azar) whose germ has become resistant to the usual anthimy drugs. With financial support from the Bill and Melinda Gates Foundation they undertook a clinical trial on 670 patients in Bihar State to prove the efficacy of the drug. A course of 3 weeks of OPD treatment with paramomycin will cost $ 21 as opposed to $ 2100 for amphoterecin which may require hospitalization.

Another example is the use of doxycycline (an off-patent drug) in the treatment of elephantiasis due to filariasis, by killing the bacteria needed by the worms, leading to their eventual death. See the Tropical Disease Initiative www.tropicaldisease.org.

I suggest that we should have a new look at off-patent generic old drugs with a view to harnessing their benefits...
fully while eliminating their harmful effects, using the recent knowledge about drug metabolizing enzymes and host genetic factors which can now be ascertained by the gene chip. These include penicillin, chloramphenicol, sulphadiazine, etc.

**Data sharing – to make effective drugs safer:** The entire debate on Patent protection and IPR with emphasis on secrecy and data exclusivity, leaves out one area of activity which needs the most urgent universal attention – viz. how to make effective drugs safer. This requires data sharing even among rivals, which is ultimately cost-saving for all involved in drug discovery and development. It is in the enlightened self-interest of even the most commercial-minded drug manufacturer to know why such a useful new anti-diabetic drug like troglitazone, approved by the USFDA after all the phase 1, 2, 3 clinical trials and sold in the market for several years with benefit to thousands of diabetic patients, had to be suddenly withdrawn due to reports of fatal hepatotoxicity in 30 patients. Today Pharmacogenomics allows us to anticipate and prevent such disasters prospectively rather than regretting them retrospectively. Human populations carry variations in genes that affect drug absorption, distribution, metabolism, target interaction and excretion. Each drug after it enters the body interacts with numerous proteins such as carrier proteins, transporters, receptors and drug-metabolising enzymes. Single Nucleotide Polymorphisms (SNPs) in the genes coding for drug targets or drug-metabolizing pathways (Cytochrome P450) are being increasingly identified, and mapped SNPs are being placed regularly in the public domain: website http://snp.cshl.org.

Genetic determinants of response to drugs can now be tested prospectively in individual patients with the help of diagnostic DNA chips, including comprehensive genotype assays for all cytochrome P450 isotypes. Affymetrix in California have developed a tiny chip that can analyze 10,000 to 20,000 SNPs to probe 6817 genes in 15 minutes. It is in the enlightened self-interest of MNCs to invest large sums of money in making these chips available to clinicians so that they can anticipate and prevent adverse drug reaction (ADRs), and save billions of dollars spent in liability for damages. It needs vision and imaginative thinking and a changed mindset to invest in DNA chips rather than in investing in promotion of their drugs (including 5 star hospitality to the doctors) which forms 40% of their expenses at present. Demand from the enlightened public and state policy should hasten the progress in this area.

India with its vast diverse ethnic population is a goldmine for this kind of research hence we should seek the Transfer of Technology for DNA and protein chips.

Like the Tsunami warning shared by different countries, alerts about drug toxicity should be shared among all scientists who are actively involved in drug discovery and development at all stages – right from the mass screening of new candidate drugs up to post marketing surveillance of approved drugs.

**Clinical Trials – Advantage India:** Most big MNCs are aware that Phase 1, 2, 3 clinical trials of new drug entities (cost estimate varying from $100 million to $600 million per drug and 8-10 years’ duration) can be undertaken in India at half the cost and in half the duration, at the same level of excellence – Good Clinical Practices, Good Laboratory Practices and full safeguard of volunteers and patients’ interest through Ethics Committees. The main hesitation of MNCs is about the protection of data through an assured legal data exclusivity mechanism. I have publicly supported this demand of MNCs and their Indian partners, since I see the tremendous opportunity for excellent clinical trials in India for a wide variety of diseases with large number of patients. In my vision the selection of volunteers for phase 1 and 2, and the selection of patients for phase 3 drug trials will not be at random as at present, but planned – based on the genotype, phenotype and chemotype, which will provide meaningful results using a much smaller sample than in randomized controlled trials. For this revolutionary approach I will insist on the transfer of relevant technology (DNA and protein chips, automatic DNA sequencers, PCR probes, mRNA expression in cancer cells) so that no blood or tissue samples (e.g. cancer tissue) are required to be sent abroad. Visionary leadership from men like Dr. R A Mashelkar and active support from the Indian Biotechnology community, can make this happen, TRIPS has many references and provisions that deal with technology transfer to developing countries. We should ensure that it actually happens.

**Discoveries vs inventions:** TRIPS has opened the flood gates to the corporate patenting of life forms as well as biopiracy. The thousands of cases of life patents and increasing evidence of biopiracy has aroused indignation and worldwide questions about the legality of the IPRs and TRIPS.

There should be no patenting of life forms which are in fact discoveries and not inventions. This includes micro-organisms of any form and biological materials found in nature or isolated therefrom, including germ plasm or any living being, naturally occurring macromolecules such as proteins, peptides, DNA, RNA, single nucleotide polymorphisms, gene fragments or modified proteins, biotechnological inventions needing the use of biological resources, stem cells, PCR techniques, machine-based embedded bioinformatics software, genomic information and genomics, proteomic, metabolomic data bases – all these should be open sources which can freely be shared.

**Learning from Computer Simulations:** The present approach of drug discovery: targeting one gene or one protein or enzyme or receptor for making an appropriate
agonist or antagonist may turn out to be too naïve and unproductive since in the living systems several genes and several protein networks act in consort. Lessons learnt from engineering hundreds of knock-out genes in bacteria and mice have shown that many of those broken genes caused no apparent abnormality. The principle of robustness is emerging as an important unifying principle in biology. Life of every kind has to cope with dramatic swings in temperature, changes in available nutrition, assaults by toxic chemicals and attacks from within and without. In order to survive and prosper, cells must have back-up systems and biological networks that tolerate interference. What most strongly determines how a cell behaves in response to a disease or a drug is not whether any particular gene is turned on or off, and not whether any particular single protein is blocked or activated, but how a constellation of genes and proteins interact dynamically in a complex network.5 We now appreciate the cybernetic relationship in cellular biochemical reactions.6 Hence the present rush for patenting a single SNP or protein or a gene with unknown function will impede rather than promote drug discovery. Patents on genetics of viruses or other naturally occurring disease mechanisms can be particularly obstructive in stopping research on new treatments as happened recently with hepatitis C virus. Biological patents are increasing worldwide and all those are pledged to secrecy, which is not conducive to the translation of new discoveries into practical medical treatment.

Keeping Science open vs Intellectual Property Rights: The UK Royal Society expressed the view in 2003 that “although IPRs can aid the conversion of good science to tangible benefits, the fact that they are monopolies can cause a tension between private profit and public good. Not least, they can hinder the free exchange of ideas and information on which science thrives”. “A good balance provides just sufficient incentive to encourage research and development but retains a high level of benefit for society”.

Medical Innovation Prize Fund is one alternative approach to patent to promote incentives for research.

In the context of drug manufacture and sale most of the talk of “Intellectual Property” is made by merchants, not scientists. In the glorious tradition of science, the thrill that a scientist gets is by sharing his discoveries with others, not keeping them secret. Material wealth decreases by sharing with others, while intellectual wealth increases by sharing. In Indian culture the deity for knowledge and learning is Saraswati while the deity of material wealth is Laxmi. We inaugurate all our scientific functions with “Saraswati Puja”, not “Laxmi Puja” (which merchants do regularly). For scientists, Laxmi is important as long as she is subservient to Saraswati. When Laxmi reigns supreme to the exclusion of Saraswati, then the whole society suffers. Then drug companies as well as doctors, politicians as well as technocrats & bureaucrats become part of the problem, rather than becoming part of the solution! As Mahatma Gandhi had said, “There is enough on this earth for everyone’s needs but not for everyone’s greed”.

REFERENCES