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Impact of industrial policy and trade related intellectual property rights on biotech industries in India

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Summary — The anticipated impacts of the liberalised industrial policy and the implications of India's agreeing to and enacting the Trade Related Aspects of Intellectual Property Rights (TRIPS) as per the World Trade Organisation (WTO) on the development of Biotechnology (Biotech) Industries in India are examined. The analysis shows that Biotech Industry will grow steadily in India due to the recent liberalisation of industrial policy and the effective promotional role of the government. The enactment of WTO will have virtually no deterrent effect on its future growth. India's becoming a part of WTO is anticipated to generate more foreign investment and would result in larger inflow of low or medium level or already adequately exploited high grade foreign technologies. Indian agriculture will be boosted by increased application of hybrids and certified seeds; enactment of plant varietal protection law as per UPOV-1978 will enable increased availability of efficient cultivars to the farmers at cost effective prices. Rights of farmers will be upheld. Introduction of many transgenic plants will be delayed due to inadequate transparency in safety. Natural therapeutic peptides used as drugs and produced by recombinant DNA technology will not be patentable as products; but the process and the genetically engineered microbes producing them will be protectable. Patented drugs will become expensive besides enjoying market monopoly. In public interest and in exceptional situations India like other countries, would be free to take necessary measures consistent with WTO to direct public utilisation of protected products by price fixation, compulsory licensing and production. WTO is anticipated to facilitate increased investment in R&D in the industry, and in more collaboration among industry and R&D institutions. On the whole, the situation of India being a part of WTO is considered to be more beneficial than being outside WTO, even though compromises would have to be made in certain areas on some principles.

Introduction

The recent reforms in the Industrial Licensing Policy and the revised procedures that have been announced by the government beginning 1991 and subsequently have profound effect on the furtherance of all sectors of the industrial activities including the Biotech industries. India's signing the final act embodying the results of the Uruguay round of multilateral trade negotiations along with 125 other countries on 15th April 1994 at a Ministerial meeting in Marrakesh, Morocco has evoked public discussion and debates all over the country regarding whether India's intentions of integration into the world economy for achieving greater international trade coherence with other countries through the enactment of liberal and uniform trade policies as per the agreement to establish WTO and implement its objectives would contribute to the healthy growth and development of Indian economy, or whether certain trade issues as well as other issues which lie outside the trade field would flare-up, and, therefore, in the long-run our decision to join the WTO will be unproductive and even detrimental. The specific issues are whether joining of WTO by India would bring in greater stability to exchange rate, improve the country's economic and financial conditions, increase national and international trade, bring in sustainable growth and development, and finally would correct and improve the balance of trade situation. Many people think that several expensive Indian developmental programmes are based on liberal monetary support from International Monetary Fund and World Bank; India's joining WTO is likely to facilitate liberal financial support from such agencies, and thereby the developmental processes would be accelerated. Others feel that expansion of market access to the benefit of all the Member Countries will eventually tell upon our balance of trade, because of the country's lower

*Views expressed in this paper are those of the author and do not necessarily express the views of the organisation to which he belongs.

level of current development, and therefore trade policies pursued in conformity with WTO would be deterrent to the domestic industries, many of which are not yet internationally competitive and thus would need deliberate protection, more than what WTO may provide for.

The anticipated impacts of the liberalised industrial policy and the major implications of India's agreeing to enact TRIPS as per WTO on the development of Biotech industries in India are broadly examined here.

Biotechnology Industry in India

In India, like in other developing countries, the term biotechnology is used in its wider connotation[1] than what is considered in the developed countries. The latter countries consider the biotech products as those which are produced by the expression of genetically engineered microbes/cell lines, and by hybridoma technology; these are viewed in India as modern biotech products. Many biotech (in its wider connotation) products are being locally consumed; a part of these is also being indigenously produced. Table 1 indicates the current consumption and the anticipated demand of different categories of products during 1992, 1995, and 2000 AD (ref.2).

The human and animal health areas which dominates the scene include production of vaccines, diagnostics, antibiotics by fermentation, bioactive therapeutic proteins including recombinant products, blood products and sustained release drug formulations including delivery systems. Agricultural biotechnology includes : hybrid seeds, plants produced by tissue culture, cut flowers (produced in controlled and contained environment), biofertilisers, biopesticides, mushroom spawns, and genetic improvement techniques of animals (including high value semen and elite embryos). Industrial products include all the fermentation based products like alcohol, organic acids, enzymes, aminoacids, starch based products, and cheese produced by using microbial rennet. Other products include biotech applications in effluent management, composting, microbial leaching and beneficiation of ores, micropropagation of forest plants, synthesis of oligonucleotides, restriction endonucleases, gels, polymers, and special materials used in Biotech research and industry. In the above category of industries there are currently about 91 units in the human and animal health area, 95 in agriculture and about 273 in industrial and other Biotech products[1]. The biotech products in 1992 contributed to nearly 0.3% of the GDP at current cost.

Table 1 — Consumption and future demand of biotech products in India*

(Unit : Rs in million)

Product category	Consumption	Estimated demand	
	1992	1995	2000 AD
Human and animal health	13750	19590	35320
Agriculture*	680	1540	3850
Industrial products	4290	5700	15000
Other biotech products	20	300	1300
Total	18740	27130	55470
(in US million $)	825	904	1849

*Excludes processed food industry and fisheries

New Industrial Policy

The management of economy and development of industry in India is vested upon the central government. With the objective of developing a globally competitive industrial sector, the central government from the Ministry of Industry substantially modified the earlier licensing policy in 1991 and onwards[3-10], and promulgated new and innovative policies for the sustainable and quicker development of industries. Certain agricultural activities were classified as industrial activities so as to enable induction of foreign technologies as well as use of indigenous technologies in industry; such activities thus became eligible for financial support from banking institutions.

Essence of Liberalised Licensing Policy

The essence of the new policy is given below :

(i) Industrial undertakings are classified according to investments in plant and machinery or total assets.

(ii) All articles to be manufactured are being described in accordance with a New Classification System, called the Indian Trade Classification System, which is based on Harmonised Commodity Description and Coding System.

(iii) Industrial licensing has been abolished for all industries including MRTP and FERA companies, and automatic clearances would be accorded subject to their fulfilling certain conditions except for certain categories of industries irrespective of levels of investment (because of their having certain special attributes related to social and economic justice and security).

(iv) Certain industrial activities are reserved for the small scale sector.

(v) Industrial undertakings should fulfill the locational policy, to avoid congestion and pollution in cities.

(vi) Foreign Technology Agreement would be automatically permitted which involves ceiling payment up to Rs 10 million, paid as royalty up to 5% on domestic sale and up to 8% on export sale, and parts paid/payable in lumpsum.

(vii) Direct foreign investment up to 51% (Foreign equity) is permitted; further increase (in%) is also possible and each such case is examined and decided on merits.

(viii) Foreign technicians could be hired without prior permission from the government.

(ix) Export Oriented Units (EOU) and units set up in Export Processing Zone (EPZ) are eligible to import free of duty their requirement of capital goods and raw materials, and these units are required to achieve some minimum prescribed "value additions".

(x) Hybrid high yielding seeds, tissue culture propagation of elite plant materials, biofertilisers and biopesticides are classified as industrial activities.

(xi) Bulk drugs involving use of recombinant DNA technology; bulk drugs requiring *in vivo* use of nucleic acids as active principles; and formulation based on use of specific cells/tissue targeted formulations would require compulsory licensing.

Impact of the Liberalised Licensing Policy

The current liberalised industrial policy has build up adequate provisions to provide necessary impetus to the entrepreneurs to set up locally competitive industrial units with the necessary support provided by the government to enable incountry industrialisation in preference to imports of finished products. In this changed environment the prospects of development of biotech industries are quite bright and several investment decisions have been taken by entrepreneurs during the past 4y. Scrutiny by the author of the industrial approvals sanctioned in the biotech sector 1991 onwards, shows that in *human and animal health area*, major investment proposals being implemented in antibiotics sector are production of penicillin-G, cephalosporin- C, and rifampicin by fermentation; in vaccine sector, recombinant hepatitis-B, oral polio, expansion in production of DPT, measles and rabies vaccines, several poultry and animal vaccines, immunodiagnostics for the detection of viral diseases like HBV and HIV, early detection of pregnancy, quantitative estimation of body hormones, cancer detection, blood grouping sera and detection devices for several infectious diseases, and fractionation of blood into cellular and other components. In the *agriculture area*, several plant tissue culture facilities have been constructed with foreign collaboration and more are in the offing; hybrid high yielding seeds and certified seeds are also being made in large quantities with and without overseas collaboration; production facilities for biopesticides and biofertilizers are also being extended. Several plant growth regulators and stimulants are being manufactured. In *industrial and other biotech areas*, plants are being set up for the manufacture of industrial enzymes (α-amylase, amyloglucosidase, invertase, protease, lipase, pectinase, and penicillin acylase), citric acid, phenyl acetyl carbinol from benzaldehyde, and restriction endonucleases, all by appropriate fermentation processes[1,2], using improved but non-genetically engineered microbes.

Thus, investment decisions in industries based on conventional biotechnologies are picking up faster. It is foreseen from these trends as analysed elsewhere[2], that during the next 5 to 8 y, there would be an investment of over Rs 8 billion in the health care area; about Rs 2 billion in agriculture; and about Rs 4 billion in other areas. The total investment of a minimum of Rs 14 billion as is being anticipated is likely to be based on imported technologies which are available for purchase; a small part of these investments would also be based on locally generated technologies. These investments and the existing ones are expected to generate biotech products of about Rs 55.5 billion by 2000 AD (ref. 2).

Implications of WTO on TRIPS

India signed the Final Act along with 125 other countries on 15 April 1994 at a Ministerial meeting in Morocco[11]. The act embodies the results of the Uruguay round of multilateral trade negotiations which was launched in September 1986 though "Declarations" adopted by the Member Countries in Punta del Este, Uruguay in Latin America and which was the most ambitious of the trade rounds under the General Agreement on Tariffs and Trade (GATT) as it covered, *inter alia*, issues related to Intellectual Property Rights (IPR).

There are seven areas of IPR which are covered by the TRIPS, namely Trademarks, Trade Secrets, Industrial Designs, Copyrights, Integrated Circuits, Geographical Indication, and Patents. In the first six areas, Indian laws, regulations, administrative procedures and judicial systems are at par with the rest of the world; the norms of enforcement and protection proposed in the WTO are in

conformity with the Indian system. In the last area, namely in issues related to Patents, Indian laws are however, substantially different from the provisions of WTO. The provisions of the latter from the Indian Patents System (Indian Patents Act 1970) are different on the following major areas :

(i) WTO provides "Product patents" in all branches of technology while Indian Patents System does not provide "Product Patents" in drugs, food and chemicals, but provides only "Process Patents".

(ii) WTO would grant patents for any inventions (whether products or processes) in all fields of technology provided they are *new*, involve an *inventive step* (non-obvious) and are capable of *industrial applications* (useful), but provide flexibility for exclusion from patentability in areas like: (i) diagnostic, therapeutic and surgical methods for the treatment of humans and animals; (ii) plants; (iii) animals; and (iv) essentially biological processes for the production of plants or animals.

WTO, however, provides *patents on micro-organisms*, and microbiological processes. In contrast, Indian patents laws do not allow patenting of any life form; however, patents based on microbial processes are permitted.

(iii) WTO requires protection of plant varieties either by patents or by an effective *"sui generis"* system or by any combination thereof, while at present there is no system for protection of plant varieties in India.

(iv) WTO provides 20 y uniform duration for coverage of patent life for all patents while Indian System provides 7 y for Food and Pharmaceuticals and 14 y for others.

(v) The burden of proof in case of infringement in WTO is substantially on the alleged infringer while in Indian System it is on the plaintiff.

(vi) WTO does not permit discrimination between imported and domestic products while according to the Indian law, importation does not amount to working of the patent.

(vii) WTO requires providing same advantage, favour, privilege or immunity granted by "a Member country" to the nationals of "any other Member country".

(viii) Compulsory licensing is permitted on merits of each case in WTO and the holder of patent will have to be heard, but Indian law provides compulsory licensing in the case of food, pharmaceuticals and chemical sector. Interpretation of Indian law implies that compulsory licensing would be freely available in these sectors.

Transition Period for Enactment of WTO

WTO provides for a general transition period of 5 y to all the developing countries for the implementation of its provisions (Ref. 11, TRIPS : Article 65 - para 1 and 2). The developing countries which do not currently provide "product patenting" as in India, will have an additional transition period of 5 y to apply these provisions (Ref. 11, TRIPS: Article 65 - para 4). These provisions of WTO have been enacted from 01 January 1995 and, therefore, India would have to implement "product patenting" in drugs, food, and chemicals from 01 January 2005 only. Products patented prior to 01 January 1995 anywhere in the world are being subjected to treatment in India based on the existing Indian Patents Laws. Applications from "Member Countries" for product patenting from 01 January 1995 onwards in India may be kept in abeyance up to 31 December 2004. During pipeline protection period (from 01 January 1995 upto 31 December 2004), however, India will have to provide exclusive marketing rights for 5 y in India for those products which are given product patents in any other "Member Countries" during the "pipeline protection" period and are in the meantime introduced in the market, provided an application is made to that effect to the government of India in the prescribed manner. The application for filing a patent for an invention made outside India for such products should have been made in any Member Country on or after 01 January 1995. Consequently the current Indian Patents Laws have been modified by a Presidential Ordinance on 31 December 1994 to suit the provisions of WTO.

Discussion

Impact of Reforms in the Licensing Policy

The reforms in the licensing policies had built, within it, several far reaching strategic implications to foster larger foreign investments in India. There is also an improvement in the public awareness of the benefits of biotechnological products and processes in health, agriculture, industrial products, and environmental management. The government is also facilitating the development of indigenous technologies by setting up demonstration units, promoting industry-institutional tie-ups and quickening the process of approvals at various stages[12]. All these factors are already showing up in terms of newer and more proposals being cleared for investments in biotech industrial sector.

Impact of WTO

Plant Breeders Rights (PBR)

On being a signatory to the Final Act, India has agreed (Ref. 11, TRIPS : Article 27 - para 36) to the idea of protecting the rights of *Plant breeders*, although, India is not yet a part of the International Union for the Protection of New Varieties (UPOV) Convention. The UPOV originally constituted on 02 December 1961, was amended on 10 November 1972 and subsequently on 23 October 1978. The amended provisions as of 23 October 1978 (UPOV-1978) are being enacted by the Members of the UPOV Union. UPOV was further modified and revised on 19 March 1991 (UPOV-1991); the revised version has not yet been accepted by the UPOV members and is therefore not yet in force. For the purpose of India, presently UPOV-1978 is relevant as the provisions contained therein may have to be enacted and implemented. The document of the Final Act requires "... *Members shall provide for the protection of plant varieties either by patents or by an effective sui generis system or by any combination thereof*"[11]. This is to be related with the existing Plant Breeders' Rights as is currently being protected globally (wherever applicable) by UPOV-1978. The provisions require that the breeders' prior authorisations are required for *production for commercial purposes, sale and marketing* of the reproductive or vegetative propagating material of the plant varieties which are legally protected. The breeders are free to make any condition for commercial utilisation of the protected varieties by others. However, authorisation by the breeders is *not required* for the utilisation of the protected varieties as an initial source material for the *creation and marketing of other newer varieties*. Thus, a protected variety is in the public domain for all purposes other than for commercial use. Breeders' protection is available to *newer varieties* of botanical genera and species, provided the variety is *clearly distinguishable* by one or more characteristics from any other known varieties, the new variety is *sufficiently homogeneous* (having regard for the features of its vegetative propagation or sexual reproduction) and further the new variety is *stable in its essential characteristics*, which implies that it should remain true to its description after repeated propagation or reproduction, or at the end of each cycle where a particular cycle of multiplication or reproduction has been defined by the breeders. All protected varieties should be given a name or a denomination by the authority providing varietal protection so that the genetic designation enables its true identification. Breeders' rights shall be protected for a period of 20 y from the date of protection provided by the authority. UPOV-1978 does not provide for granting patent for protected varieties, i.e., double protection is not permitted. For enacting UPOV-1978 the Government of India will constitute the enabling machinery and mechanism on or before 31 December 1999.

Farmers' Rights and Researchers' Rights

Evolving an effective "*sui generis*" system for the protection of invented plant varieties and seeds as per the provisions of UPOV-78 will not take away the "Farmers' Rights" and "Researchers' Rights" to use protected plant varieties and seeds as these activities *per se* are not commercial activities. The farmers shall be able to raise their own seeds and retain them even to distribute them in exchange, among the village community as per the existing traditional system. The researchers shall be able to generate newer varieties for commercial purposes from the protected varieties. Implementation of UPOV-91 will take away these rights from the researchers; however, the farmers will continue to have their rights as said above.

Hybrids and High Yielding Seeds

For enabling the farmers to use the hybrid F1 seeds which are raised by using proprietary parental lines, the F1 seeds would have to be purchased by the farmers every year as their (farmers') own generated F2 seeds and further generations, would be less productive than the F1 seeds/varieties. In situations, where productive vigour and modified properties are naturally maintained for several generations through inbreeding, the provisions of protection of WTO would not substantially be contrary to the interests of the farmers as they would have to buy the improved seed variety once only, and subsequently they would be growing their own seeds for own use or for exchange in accordance with the traditional system.

The situation of purchasing productive hybrid F1 seeds for increasing production of every crop of several vegetables in crop season is already in existence, even though India does not have any plant protection law for the breeders. The breeders maintain their technological secrecy by growing their parental lines at various strategic locations and countries, and sell the F1 seeds world over. Indeed when WTO is implemented and India enacts the provisions of WTO, there would be increased local production of F1 seeds for several such varieties as these would be *legally protected*. It is expected that with more availability, the prices of many of such productive seeds may come down. It is further mentioned that although the current prices of hybrid seeds of tomato, brinjal, capsicum, cucumber, bittergourd, and pumpkin sold internationally including in India, are much higher than the correspond-

ing natural ordinary seeds, the current cost of one hybrid F1 seed for fruits and vegetables works out in India, to be within 8-12 p and that for cucurbits between 15-20 p;a hybrid F1 seed-raised plant is thus inexpensive to the farmer. By plant tissue culture methods, through which hybrid F1 plants could be mass multiplied, it is not yet possible to produce a F1 plant at a price less than Rs 1. The production methods of hybrid F1 plants by cross pollination using proper parental lines would thus stay, and would continue to excel over plant tissue culture methods of propagation from economic and physical performance aspects. Further, as the international selling prices of cross pollinated hybrid F1 seed-raised plants are well within the reach of the cultivators, the concern that hybrid F1 seeds would be expensive and unaffordable by the cultivators does not seem to be tenable. In situations where hybrid F1 seeds would cost substantially more than the corresponding natural ones, such F1 seeds would have to win the economic battle by assuring and performing better in terms of production, productivities and/or other economic gains to the user. The cultivators cannot be lured to purchase such seeds only on the assurances of substantially better performance over the existing varieties by marketing propaganda; they would have to be satisfied by demonstrating performance in fields. Quality control in the sale of seeds would therefore become more imminent specially for branded seeds.

Transgenic Plants

It is a matter of concern that several transgenic plants would emerge from high tech companies with specific advantages like resistance or increased tolerance to plant viruses, pesticides, soil and water salinity, water stress and draught, modified fruit ripening traits, altered composition of plants/fruits etc. All such plants are *expected to be proprietary ones* and WTO system *shall enforce their protection*. It is believed that such plant varieties may have considerable advantage in agricultural practices but may be very expensive in India. So far, although nearly 900 transgenic varieties have been tested world over, only one transgenic plant and its fruit namely delayed ripening and better flavoured tomatoes have come into the market recently in the US from May 1994 (ref.13). These fruits have been introduced by Calgene Inc., USA and have been highly priced compared to the existing varieties. Calgene have voluntarily provided description of techniques used to produce these tomatoes although they were not obliged to do so as per the US Food and Drugs Act (USFDA) permissions. However, humans are yet not open to using these fruits freely as the notional ill effects of the long-term use of these fruits in humans have not yet been fully resolved and cleared from the minds of people. It is nevertheless foreseen that these tomatoes will eventually be popular. Time will tell how these would be accepted by humans.

Transgenic plants invented and tested world over lay emphasis on the development of herbicide tolerance, insect resistance, modified traits, altered composition of plants/body parts/fruits (in terms of proteins, carbohydrates, fats and oils), and microbial resistance. Herbicide tolerant transgenic plants top the list of plants being field-tested and the target crops are *corn, soyabean, cotton, tomato, potato, alfalfa, peanut, rapeseed mustard, rice, wheat, beet, barley, bentgrass, lettuce and tobacco*. During the period 1986 to 1994, many crop plants experimented in more then 14 countries including the US, the UK, Switzerland, Sweden, Netherlands, Belgium and Japan were for producing engineered varieties tolerant to chemical herbicides; nearly 57% of the transgenic plants field-tested were for chemical herbicide resistance, 13% for plant virus resistance, 10% for insect resistance, 5% for male sterility, and the remaining 15% for quality traits, disease resistance[14].

Herbicide tolerant plants are created either by inserting genes that detoxify the target herbicides or by modifying the sensitivity of the plants to the herbicides. Genes from the resistant microbes are isolated and inserted after suitable modification into the target plants/crops so that when such plants/crops are exposed to the specific herbicides, the genes get activated and detoxify them. In the other strategy the procedure is to desensitise the herbicide acting sites in plants. In all these strategies, *genes foreign to plants are inserted into them to express, wherever the plants come into contact with herbicides. Introduction of transgenic chemical herbicide- resistant plants in agriculture will* increase the chance of transfer of transgenes from crops to near-relative wild plants and thereby may transform wild weedy plants into new worse-than- the-present weeds, the management of which may be different and may require newer chemical herbicides to be invented.

Virus resistant transgenic plants are invented by incorporating coat protein genes of plant viruses into the genome of the target plants[15]. The transformed plants synthesise the mRNA complementary to the viral gene which in turn translate the synthesis of viral coat protein and thereby prevents the virus from infection — a phenomenon commonly known as *coat protein mediated* protection. *Use of such transgenic plants may lead to the development of new strains of viruses through recombination between the viral genes contained in the plant and another infecting virus*[16]. There is indeed great

concern among researchers about the risks of introducing virus-resistant crops and it is strongly felt by a group of scientists that risks must be adequately assessed before such plants are commercialised[17].

Insect resistant transgenic plants developed, e.g., by inserting the genes from the bacteria, *Bacillus thuriengiensis* (Bt) would produce insecticidal proteins specific to certain families of insects like lepidopteran worms, and coleopteran beetles, and these insects on ingestion of such plants would be killed by paralysis of their epithelial cell lines of gut and rupturing of the digestive tract thereby releasing the highly alkaline food products into the body of the insects and destroying them. In this strategy, of the different natural strains of Bt, the one known as *B. thuriengiensis var kurstaki* which produces lethal proteins toxic to lepidopteran insects from several single individual genes and which individual proteins had been found to be non-toxic to humans and mammals in limited laboratory trials, had often been chosen as gene sources. The natural individual gene had further been truncated to enable higher expression of the natural toxic proteins, and then using strong promoters, the new gene constructs had been inserted into Ti plasmids and the modified Ti plasmids were inserted into the disarmed *Agrobacterium tumefaciens*, and the latter, which is a bacterial pathogen to dicot plants, had been used to infect various target plants. Back-crossed transgenic plants, e.g., *produced by inserting Bt genes and field tested did not resist the damaging of plants by major lepidopteran pests*[18,19]. From the collections of Bt strains, at least nine distinct toxic proteins have been characterised which are toxic to lepidopteran pests[20]. It has been demonstrated that there may be different receptor sites for different Bt toxins even within a single insect pest[21-23] and the toxicity of these proteins is believed to be due to their different degrees of binding ability to the receptor sites in the larval midguts, which obviously vary considerably among the toxic proteins. Added to these findings, it has further been found that resistance is toxin-specific. Thus, Indian meal moths which were more than hundred times resistant to Bt toxin from CryIA(b) gene were not resistant to Bt toxin from CryIC (ref.24). Similarly for Diamond back moths which were not resistant to CryIB or CryIC proteins, were more than 200 times resistant to CryIA(b) proteins[25]. The basis for resistance development may thus be related to the inherent difference in the receptors of insect midguts, besides other factors, and are obviously complex phenomena, the solutions of which are not likely in near future. In the meantime, more than 50 patents had been taken in the US alone on various Bt strains isolated from soil[26]. However, the ecology of Bt and its role in nature is mostly unknown[27]. Foliar applications of commercial formulations of Bt sooner developed resistance in field population of major lepidopteran pests of vegetables[28]. *Transgenic plants developed with several Bt genes and by deploying tactics to control pests eventually did not offer clear advantages in most of the situations*[29]. Despite such scientific findings, R&D strategies for producing transgenic Bt plants of several target crops and vegetables have been taken up by many multinational companies world over and several such plants have made considerable progress in limited field trials and are on the verge of large-scale introduction; these are receiving serious considerations from the industrialists and the agriculturists for field applications world over. However, from the available field results, these plants are not seen as causes for optimism. Transgenic plants eventually developed and introduced in agriculture after obtaining the necessary statutory permissions are foreseen as not to last for more than a couple of years even by deploying different tactics for delaying the development of resistance, as field resistance would develop much faster than is often surmised. The available data on Bt gene incorporated transgenic plant experiments seem to demonstrate that insects control through the development of transgenic plants is a distant dream. Added to these surmised shattered hopes are uncertainties about the ecological changes and their effects on humans that may be brought in by the excessive use of Bt gene engineered plants in agriculture. Safety issues will remain unresolved and unanswered for long.

During the evolutionary process, nature choose to separate the plant kingdom from the animal kingdom by differentiating the constitutive nucleic acid stretches in the genomes with separate marker molecules so that these classes of life forms moved with time in orchestrated rhythm. Plant pathogens had not been animal pathogens and *vice versa*. Through the millions of years of journey of life in the planet earth this discipline had almost rigidly been maintained by nature for reasons best known to it. It is only from the late 70s that human intervention started in moving hitherto unrelated genes from bacteria to plants or viruses to plants or animals to plants, etc. *The impact of such unnatural mixing of genes* and the possibility of creation of newer life forms by hybridisation along with the consequential effects of such life forms cannot be predicted by humans so early. Therefore the extensive use of such unnatural engineered plants is expected to be delayed by the society for years to come, except in situations where transgenics have been developed by altering or moving *related genes* into plants for generating transgenics with say, better flavour characteristics or delayed ripening traits or plants having fruits with higher nutritive values, etc.

In such situations, significantly greater exploitation of trangenic plant varieties over the existing natural ones by human kind is not foreseen in the near future. It is surmised on the other hand that there would be greater exploitation of the already established natural plants and seeds which have higher productivities and/or have concurrently better performance characteristics in adverse situations; these natural varieties are not patentable by WTO provisions. Many natural varieties as well as somaclonal variants would also be developed from the existing gene pools by use of essentially biological processes.

Plants Containing Patented Genes

In situations where useful genes modified by human intervention would be invented (which would be patentable as per WTO), and which would be inserted into plant varieties for imparting improved properties (e.g. herbicide resistance, plant virus tolerance, better fruit characteristics, etc.) the resulting plant varieties *will be new*. In accordance with the provisions of WTO, such plant varieties would have to be protected. However, as per UPOV-1978 plant varieties protected by a *sui generis* method would not be patentable, as double protection is not permitted in UPOV-1978. Further, WTO provisions also provide freedom and choice to countries not to patent plants and animals. Varietal protection under UPOV-1978 provides *rights to public* to use the variety for generating and selling developed newer varieties. As the protected varieties indicated above would contain patented genes in them, the situation does not indeed provide protection to the patented genes insofar as development of new varieties is concerned. This advantage could be availed of while enacting Plant Breeders Rights in India as per UPOV-1978. The UPOV-1991 is much stringent and the implementation of its provisions will take away the advantages given above. Therefore, delay in the enactment of UPOV-1991 by the Member Countries would provide more freedom to them and is expected to help the world community more, in general.

Need to Protect Natural Gene Pool

The developing countries with access to a wide spectra of germplasms are taking steps to enact laws to preserve their biological diversities, and therefore commercial exploitation of such varieties by others is likely to require suitable compensation to the original possessor of such germplasms, once biodiversity protection laws are enacted. It is foreseen that as India has vast biodiversities and natural germplasms, there would be collaborations among *businessmen and R&D institutes/companies* for extensive screening of the biological diversities for hitting at efficient natural products useful for human therapies, productive agriculture and environmental protection. It would be in the interest of the country to operate such collaborations with proper security to India for sharing the benefits that may accrue from new discoveries. As far as possible, working on natural germplasms may be through statutory authorities and international bodies, which may act as repository to valuable germplasms originating from India.

Patentable Microorganisms

Taking advantage of the freedom provided in the WTO, India may decide not to accept patenting of any life form classified as animals or plants but would have to agree to the patenting of micro-organisms . This situation may deprive India in being able to produce by duplication other patented processes, substances such as bioactive therapeutic products/proteins produced by genetically engineered micro-organisms, as such micro-organisms may be patented elsewhere. However, if the products produced by microbes are "natural" substances produced in living bodies, such products may also be excluded as per WTO provisions and may not be patentable in India. For example therapeutic proteins like insulin, erythropoietin, epidermal growth factors, interferons, interleukins, GM-CSF, G-CSF, growth hormones, thrombolytic proteins like streptokinase, urokinase, and tissue plasminogen activator, which are natural substances and which may have been discovered, or such other natural substances which may not have yet been discovered but would be discovered in future may not be patentable as "products" in India if the law is so enacted, as these would be treated as "natural" products. On the other hand, the expression hosts as micro-organisms designed by human intervention through the process of genetic engineering which are not available in nature and the design of which is non-obvious, would be patentable under WTO. There is, therefore, a need to define and categorise *Patentable microorganisms* required as per the WTO. Microorganisms as per the classical definitions are organisms too small to be visible to the naked eye; organisms include all the living things which may be a single cell or a group of differentiated but interdependent cells. The studies of microbiology include the interaction between human and microorganisms, plants and the microorganisms, environment and the microorganisms, etc. Microorganisms include *viruses* which depend entirely upon the machinery of reproduction of the host cells and which are not visible under a light microscope (LM) but which could be viewed under electron microscope (EM); *bacteria* which lack a true cell nucleus and therefore their genome lie within the cytoplasm, and

further bacteria are visible under LM and they reproduce primarily by binary fission; *fungi* which are larger than bacteria and have advanced cell structures and their genetic material is clearly separated from the cytoplasm by a nuclear membrane and further some of them reproduce by budding while others form growing colonies of attached organisms; and *parasites* which include the protozoans and various multicellular eukaryotic organisms all of which undergo complex life cycles which may involve several host species. Ordinarily microorganisms *do not* include various *tumour forming* cell lines and *monoclonals* as these are not natural organisms but are produced under abnormal stress conditions or under human interventions. Moreover, most of the transformed cell lines and all the monoclonals are derived from cells/tissues of vertebrates, which are not considered as microorganisms. Patentable microorganisms would be those which have been produced by human interventions and where the interventions are non-obvious and further that they do not involve an essentially biological process. It is obvious that *patentable microorganisms* are those natural microbes which have been modified by human interventions and may include the transgenic viruses, bacteria, fungi, and parasites. They may not include the tumour forming cell lines and the monoclonals. Once a transgenic microbe is patented, it would not be publicly available without exploiting the patent.

Patentable Natural Substances

Natural genes, nucleic acid sequences unmodified but discovered from natural substances, or any other useful products isolated from natural substances may also be excluded as per WTO and may not be patentable as "products" in India, if the law is so enacted as these products are natural ones and their discovery does not involve an inventive step. However, modifications to these substances which are non-obvious and which could be considered as inventions (involve an inventive step) would be patentable as "products" in India under WTO regime. The later provides scope for patenting *modified natural substances* which may be more useful. However, the nature and extent of human intervention needs thorough study and when only trivial methods may have been used (which are obvious) in the making of the so called modified natural substances, these could be excluded from patenting as products, e.g., simple derivatisation of natural products. However, many modified natural substances may be invented, involving distinct inventive steps and patented in future, and many of these may be produced by genetic engineering methods. Such patented substances which may be useful to humans will not be available for compensation-free use and, therefore, will not be in the public domain. Indian government anticipated such risks and hence emphasized on in genetic engineering research from the late 80s. Research projects had been funded in eminent institutions and centres of excellence to generate indigenous capabilities led by Department of Biotechnology (Government of India) along with other funding institution like Department of Science and Technology (DST), Council of Scientific and Industrial Research (CSIR), Indian Council of Medical Research (ICMR), Indian Council of Agricultural Research (ICAR), and Department of Scientif. and Industrial Research (DSIR). Transformed expression hosts in *E. coli*, Yeasts, Streptomyces, *Bacillus megaterium*, *Spodoptera lutera*, Baculovirus, Vaccinia virus, *E. coli* Phage M-13, *Agrobacterium tumafaciens* with modified Ti plasmid have been developed which have been designed to express different value-added proteins. However the expression levels as well as the knowledge base for arriving at the final products (downstrean process) are still at a low level and are far away from commercial exploitation stage[1,2].

Indian industrialists would, therefore, have the option of using non-patented microbes if available, or of designing newer transgenic microbes or cell lines or life forms through specialised scientific inputs to produce such valuable substances as mentioned earlier by the process of genetic engineering/ recombinant DNA technology. Such inventions would need expenditure of sizeable sums in R&D.

R&D Funds and Needs

It is estimated that R&D funds from all sources that are available for biotech research are currently only about Rs.1100 million per annum of which more than 85% comes from the government agencies[1]. Sufficient funds from the private sector are not yet forthcoming. The government funds are available only to the public funded institutions and universities where emphasis is laid on research in basic sciences. Private Indian entrepreneurs would have to take off from the leads available or generated from the basic research and would have to substantially invest and concentrate on developing innovative processes for patent expired biotech products to come up as an alternative source of supply of products to make the market competitive. It is, however, foreseen that research directed towards the development of "new molecules or products" from India would be extremely difficult as it is anticipated that the R & D costs for such developments which according to various estimates vary from Rs 500 million to Rs.7000 million per product would not be available for deployment. The often quoted capitalised

cost of US $ 231 million in 1987 (ref.30) for one new marketed drug might have increased further in the International arena in 1995. Added to this, the annual increase in the expenditure in research in 1993 had also gone up particularly in the developed countries *more than* the corresponding annual increase in sale; in Germany, research spendings increased on an average by 15.4%/y from 1980 to 1990 while sales increased by 12.7% (average). Nearly, US $20 billions were spent world over in 1990 on pharmaceuticals R&D. Analysis of data on R&D spending and sales of top 30 international pharmaceutical companies (comprising 12, 13 and 5 European, the US and Japanese companies, respectively) revealed that the European, the US, and Japanese companies had spent 16.1%, 14.3% and 12.1% respectively of their sales turnover during 1993 (ref.31). This expenditure provides an indication of the quantum of money involved in new drug discovery, development and commercial introduction. These figures are, however, primarily based on spendings on *new synthetic drugs*; new drugs in the arena of biotechnology which may be dwelling in difficult therapeutic areas like thrombolytic agents, endocrine disorders, genetic diseases, various types of cancers, nervous and brain disorders, and severe systemic infections *may require to cross bigger innovative hurdles and more stringent registration requirements*, and, therefore, may need larger sums for R&D. Added to these, the health authorities are trying to harmonise the drug registration procedure keeping human safety and therapeutic efficacy on the forefront, and thus the expenditure on clinical trials ever increased over the other components of research costs, namely drug discovery, biological and pharmacological research, pharmaceutical formulation development and pharmacokinetics, toxicity studies, and other costs (including patenting, documentation, and registration). It may also be noted that new innovations in biotech which require trained manpower, research material, and efficient infrastructure are all available in some of the developing countries like India, Brazil, and China where the manpower is far more cheaper than that in the developed world. Amount needed for new drug discoveries in these countries is therefore expected to be much less; in India the cost may be 5 to 7-times lower according to the author. Indeed, Indians have discovered and developed up to 1994, a small number of about a dozen of drugs like urea stibamine for Kalaazar, Methaqualone (hypnotic), peruvoside (cardiotonic); hamycin (antifungal antibiotic), centimizole (antithyroid drug), sintamil (antidepressant), tromaril (antiinflammatory drug), cibemid (anti protozoal), gugulipid (hypolipidimic drug), centbucridine (local anaesthetic), centbutindole (neuoleptic) and centchroman (contraceptive), and some diagnostic devices based on sound immunological principles at much lower costs. It is estimated that the cost of discovery and development of a new biotechnology based drug development may be in the range of Rs 1000 - 1500 million (about US $30-45 million) in India. These costs are much lower when compared with discovery costs in the developed world, but yet such huge amount may not be so easy to obtain in India. It would also require considerable efforts to attract international companies to use the Indian base for new drug development. The WTO regime would, therefore, lead to the creation of monopolistic situation for new products which is foreseen to be invented primarily in the developed world only.

Patented Products and Alternatives

New products protected with exclusive rights would obviously be available expensively during patenting of such products. However, if one analyses the rate of global new inventions, it could be seen that annually very small number of newer products in the field of drugs are introduced into the world market.

According to one estimate, at any given time, usually not more than 10-15% of products available in the market (in value) are covered under patents[32]. According to the other, patented drugs constituted only 8.4 % of the total Indian pharmaceutical market[33]. Thus, non-patented products could significantly serve as alternatives to feed the requirement of the people. Keeping in view these facts, the concern that all products would become expensive under WTO regime is not feasible. It is further mentioned that the prices of the existing products would not fluctuate substantially under the WTO regime as the market competition which is the dominant force for stabilizing market price will not be affected or altered by the introduction of WTO for the existing products. In addition, the low purchasing power of the average Indian and the existing statutory Drugs Price Control Order will also serve as control for excessive price increase, and these factors are virtually inert to the influence and provisions of WTO. Further, by enacting the provisions of WTO, the Indian laws will not protect the existing products which are covered by patents elsewhere or even those on which patents have been obtained but they have not yet been introduced in commercial markets. WTO has been enacted from 01 January 1995 and as mentioned earlier, there is an incubation period of 10 y up to 31 December 2004, up to which Product Patents may be excluded in India. From 01 January 1995, the relatively small number of patented products which are not produced in India and the technologies for which have not yet been developed locally, would be expensive, as their pricing would be

decided by the Patentee or its Assignee who would demand the maximum, to the extent the market would be able to bear. It appears, however, that the consumption of such products will remain low for some time due to price disadvantage and further due to our options of resorting to the less efficient alternatives.

Impact of Product Patents

Product patents in the long run would tend to sustain higher prices of patented drugs and such effects are expected to be significantly visible from 2005 AD. Indeed, it has been shown that the prices of drugs decline substantially, once the patent expires[34]. However, introduction of product patents is also expected to bring in higher efficiency and productivities by the induction of newer technologies, increase in foreign investment, more pressure on local R&D set-up resulting in higher rate of local innovation, a higher rate of international innovation leading to eventual increase in global competition, reduction in production inefficiency and improvement in the quality of drugs/products. If in the changed scenario, India does not tune up to resonate and perform, there could be possibilities of displacement and closure of inefficient local companies, and replacement by efficient foreign companies, a situation with far reaching consequences which holds potential threat to destroy or at least inactivate the accumulated learning of local companies, R&D institutions, etc. The worst scenario must be kept in view and plans including R&D thrusts must be drawn out at national level to become reasonably competitive on a long term global perspective.

Concerns have been expressed that "product patents" would "stop" research on "newer molecules" that would be invented and used in future for a period as long as the product is protected by a patent. Since product patents would include drugs and pharmaceuticals too, such concerns have strong political, sociological, and medical issues, besides economy. Indeed the economic issues in such situations take a back seat and products used as drugs are forgotten to be commercial items which legitimately should also be considered as sources of profit, trade, employment, and economic gains. It is recognised that the price of products comes down when there is a strong competition in the market place. Patents avoid competition and promote monopoly. It is, however, to be considered that products invented as drugs and protected by patents take nearly 10-15 y of labour with massive investments to generate volumes of safety and efficacy data before they are actually marketed as drugs. Societies cannot take chance on the adverse effects of drugs without actual trials conducted on humans. Such efforts need to be rewarded to the extent these are considered legitimate. The actual residual life of new drugs is expected to be between 5- 10 y and consumers other than the inventors may have to pay higher price for the inventions for their "residual patent life".

For remaining competitive in the global market for biotech products on which patents are going to be expired, India from the private sector could perhaps adopt a strategy of developing and perfecting processes of such biotech products in its own R & D and could introduce such products just after the expiry of the patented period. This strategy would be competitive and may cost between Rs 10 million to Rs 100 million/product. Such lower costs are primarily due to the substantial savings in initial innovative costs and further marked savings in the cost of generation of safety and efficacy data.

Need for Teaming Up Between Industry and R&D Institution

India has a large pool of skilled work force and has concurrently invested considerable sum in government funded national R&D institutions and universities. These are showing results in terms of reasonably good levels of scientific publications in all areas, including biotechnology. However, the scientific results are not yet getting translated into products and processes, as the institutions do not really have commercial capabilities. In the changed situation after the enactment of the provisions of WTO, Indian industrialists will be in disadvantage, specially in modern biotech sector which is highly scientific and involves skill, if they do not become innovative. Indian industrialists will do better by collaborating with national laboratories and universities for conducting joint research, as this would supplement the efforts of each; besides, the collaboration will be considerably cost-effective. In new biotech products, requiring the use of genetic engineering there is no scope for escape from local capability building through our own R&D efforts.

Reversal of Burden of Proof

The requirement of "Reversal of Burden of Proof" for alleged infringements for "process patents" as embodied in WTO (Ref.11, TRIPS : Article 34-1b) would require the owner alleging infringement to establish that he has been unable to find out the process actually used by the defendant for the same or similar products marketed, despite best efforts. But there has to be arguments to raise doubts that there is likelihood that the process used by the alleged infringer is patented. Once this is established in the court of law, the alleged infringer after protecting his business

secrets and the details of the manufacturing processes can defend to establish that the process used by him is different from the patented process, if that be the case. This clause of WTO would, therefore, not create any major topsy turvy in the business activities in the country.

Implications of Importation Amounting to Working of Patents

As WTO does not permit discrimination between imported and domestic products and as per WTO provisions, importation would amount to the working of patents (Ref.11, TRIPS : Article 27 para 1), concerns have been raised that through these provisions many innovative products, invented elsewhere, would only be available as *finished products* at higher prices. Biotechnological products are highly skill based commodities and are often subjected to deterioration in hostile climatic conditions and unskilled handlings. Often, an efficient cold chain and proper manners of use are necessary, specially for drugs and pharmaceuticals. It is surmised that many new products which may be invented elsewhere may not be efficiently marketable in India merely by appointing distributors who usually are not sufficiently scientifically trained. These factors would be telling upon the decisions of foreign producers marketing labile but effective biotechnological products in India through exports, and distributions effected through local agents. There would be several favourable points in the setting up of local production facilities for easing the distribution of products, as India has a large pool of trained manpower, most of the capital equipment are locally available and in deserving cases import of "Capital Goods" has been eased out, and further a local company would not only cater to the large Indian needs but could also use Indian base for exploiting the Asian and the neighbouring markets. It is therefore anticipated that when important life saving biotech products would be introduced in India which are covered by Patents, the Indian industrialists would initiate dialogue with the exporters of such products holding the patent rights, to have collaboration with Indian counterparts to eventually provide further support to the patent holder to exploit the patent more extensively by enlarging the market and by inducting the technology for local manufacture for mutual benefits.

Most Favoured Nation Status

By joining WTO, India would receive the *Most-Favoured-Nation Treatment* (Ref.11, TRIPS : Article 4) from all the Member Countries and, therefore, there would neither be any need to specifically enter into bilateral collaborations with any Member Country for international trade, nor any Member Country could impose special sanctions to destabilise international trades of India.

WTO Safeguards for Over Exploitation of Patents

The provisions of WTO provide for authorisation of use of a patent by the government or by parties authorised by the government including Compulsory Licensing, and such authorisation is guided by certain conditions such as situations of National Emergency or circumstances of extreme urgency or in cases of public non-commercial use (Ref.11, TRIPS : Article 31). The scope and duration of such use will be limited to the purpose for which it was authorised and further such use will be non-exclusive, non-assignable and shall be for domestic market only. These provisions are safeguards for over exploitation of patents concerning products/processes in areas of public health, nutrition and other major areas of public interest.

WTO — A Compromise Package

WTO is eventually a compromise package among different Member Countries, and the signatories to the Final Act have agreed to adjust in accordance with the provisions of WTO to derive maximum benefits of sustainable development through the process of integrated economic globalisation by liberalising and agreeing to adopt *at least the minimum provisions* as set out in the WTO (which are the floor limits to be enacted upon) for enabling smooth global trade among Member Countries, although individual Member Countries are free to enact their own laws more stringent than the provisions set out in WTO. The ceiling limit has not been spelt out in WTO.

Concluding Remarks

Conventional biotech industries will grow steadily in India and WTO will have essentially no deterrent effect on its growth. Indian agriculture will use more of the highly productive hybrid seeds and certified seeds which would be available in adequate quantities. Local developments in the production of hybrids and efficient parental lines through conventional methods would also be significant. Use of productive seeds along with the application of proper agronomic practices will increase and thereby Indian agriculture will be modernised, and will improve over the years. The concern that modernisation on Indian agriculture may be threatened because of protection of newer varieties[35] does not seem to be real. Use of many transgenic plants is expected to be delayed for reasons of inadequate transparency in safety.

Health care products produced by the use of efficient microbial processes, genetic engineering, and hybridoma technology will be expensive in India after the enactment of WTO. This situation cannot be prevented for long, since the local developments which could pose threats to the monopoly are yet at a low level.

Genetic engineering technologies and new products derived therefrom in all sub-sectors of biotechnology would be in the hands of a few companies. These companies would develop and perfect such products often by collaboration with or by acquiring of several classes of companies, besides developing relations with R&D centres of excellence. The financially sound companies would eventually control such endeavour. Technologies for new products successfully launched elsewhere would not be available for purchase for several years in the future, and such new products would continue to be expensive. Many years later, eventhough the developing countries like India may generate local capabilities, the developed world would have moved ahead further and therefore the technological gaps will widen, and it is surmised that eventually the world would be polarised in new biotech products, and thus such products would continue to be available at higher prices to the developing world.

Technologies are becoming increasingly R&D intensive. R&D investments generate intellectual properties which are to be protected, and the WTO system which recognises such needs by rewarding and encouraging innovations has been accepted by all the Member Countries. In exceptional situations, to promote and adequately protect public interest, India is free to adopt measures consistent with WTO to direct authorisation of use of such patents which may adversely hinder the causes of public interest. In the emerging situation, following the enactment of WTO, R&D base of the industry will also be strengthened, and greater collaboration between Industry and R&D Institution is foreseen in the country specially for developing innovative processes for patent expired products and for exploiting the naturally occurring biologically active substances.

India being a signatory to the Final Act embodying the results of the Uruguay round of multilateral trade negotiations, would eventually be beneficial eventhough India had to compromise in certain situations. By being a part of WTO, it is anticipated that there would be more foreign investment and more in-flow of foreign technologies; the industrial as well as the agricultural production related to biotech areas will increase.

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