Review Article

Status of the Indian biopharmaceutical industry and way forward to be a dominant global player

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Abstract

The government promotes biotechnology in India, with the Department of Biotechnology (DBT) taking the leadership role, whereas some other departments also join in the endeavor. Modern biotechnology is no more new to India. Several therapeutic and diagnostic products are manufactured in the country from the primary stage. The emphasis is on the manufacture of patent-expired products more cost-effectively. The Indian biopharmaceutical market was approximately INR 32261 crores (US$ 4.032 billion) during 2021–2022 and approximately 1.14% of the global market. The manufacture of biopharmaceuticals needs sophisticated equipment and specialized skills. India has acquired skills in recombinant deoxyribonucleic acid (rDNA) technologies, developed capacities in genetically modifying *Escherichia coli*, *Saccharomyces cerevisiae*, *Pichia pastoris*, *Hansenula polymorpha*, and Chinese hamster ovary (CHO) cells lines, and has expertise in the multiplication of viruses in different animal and human cell lines. India produces many therapeutic and diagnostic recombinant proteins, including several therapeutic monoclonal antibodies. The more advanced areas of biopharmaceutical technology, such as mRNA-based cell therapies, including in-vitro modified somatic cell-based treatment and chimeric antigen receptor (CAR) T-cell therapy, are evolving. Genome editing technologies involving the manipulation of germ line cells are in the research and development (R&D) stage. Xenotransplantation technologies and the development of humanized transgenic animals are yet to start. Appropriate artificial intelligence programs may be included in the Indian biopharmaceutical industry to speed up the development of novel biopharmaceuticals. There are shortages of leaders adequately trained in biopharmaceutical skills in manufacturing, and the industry has constraints of abundant infrastructure and finance for deployment in R&D. India is committed to fulfilling a social objective by providing many essential medicines, including biopharmaceuticals at affordable prices through the Pradhan Mantri Bhartiya Janaushadhi Pariyojana.

Keywords: Artificial intelligence, biopharmaceutical industry, biopharmaceutical market, biopharmaceutical skills, biopharmaceuticals, genome editing technologies, mRNA vaccines, xenotransplantation

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INTRODUCTION

After the coronavirus disease-2019 (COVID-19) catastrophe, a recession period prevailed over major sectors of the business category, resulting in reduced enthusiasm for investment in new ventures worldwide. India tackled the emergency relatively well by producing effective vaccines and diagnostic devices locally and taking steps to vaccinate people nationwide by adopting an elaborate program.[1] The post-COVID-19 environment is changing fast, and

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some industry sectors, like the biotech business area, are boosting vibrancy. Hopes for availing of the opportunities emanating from discoveries in the diagnosis and treatment of infectious microbial diseases, treatment of systemic defects in body parts, and management of chronic and life-threatening diseases in the healthcare area; raising the productivities in agriculture; the use of green technologies in the industry to reduce pollution; and the utilization of degraded and wastelands by using stress-resistant plants or treating solid and liquid waste using microbes and plants, etc. in the large spectra of biotech business are rising fast among the entrepreneurs. In this article, concentrated efforts in the biopharmaceutical business are being focused on. Biotechnology in the pharmaceuticals sector applies techniques developed through basic and applied research, using biological materials to produce, identify or design drugs and pharmaceutical substances and to modify and use living organisms, including microbes and human cell lines, for human benefit. Biopharmaceutical substances are medical products. These comprise proteins, carbohydrates, nucleic acids, lipids, and living or inactivated cells or tissues and are produced in recombinant living substances such as plants, viruses, bacteria, insect cells, and animal cells, including human cells. Bioactive substances require the isolation of active substances in pure forms and are separated using complex purification methods.

PROMOTION OF BIOTECHNOLOGY BY THE INDIAN GOVERNMENT

Modern biotechnology is no more new to India. The whole sector, conventional and contemporary, has been promoted mainly through government departments like the Department of Biotechnology (DBT), Department of Science and Technology (DST), Department of Scientific & Industrial Research (DSIR), Ministry of Agriculture, Ministry of Health, and a few other departments. The money has been utilized to promote all aspects of biotechnology, including manpower development, setting up of primary and application-oriented research institutions, funding for research, promoting the development of technology and technology transfer, providing assistance to small and medium entrepreneurs, liberal intellectual property protection within the provisions of Trade-Related Aspects of Intellectual Property Rights (TRIPS) of World Trade Organization (WTO), setting up rules and procedures for fostering the growth of biotech industries on a precautionary principle; improving public health by providing essential vaccines free of costs, covering the pregnant women and the newborn through the promotion of Universal Immunization Program and the like. Public institutions of the DBT, DST, Council of Scientific and Industrial Research (CSIR), Indian Council for Agricultural Research (ICAR), Indian Council for Medical Research (ICMR), the University Grants Commission (UGC) and the All India Council for Technical Education (AICTE) had promoted different aspects of biotechnology by being involved in multiple tasks and activities. To promote biotechnology in India, the government created the DBT in February 1986. According to the author's estimate, the combined expenditure for promoting biotechnology in the country, starting from February 1986 up to December 2022, is estimated to be over INR 15,000 crores from the Government alone.

INDIAN BIOTECH INDUSTRY

During the last two decades, several private industries have made considerable investments in modern biotechnology; earlier, there had been a sizeable investment in conventional biotechnology activities. Traditional biotechnology industries in India are more than 100 years old; the products include fermentation-based substances, including alcohol; sera and vaccines; antibiotics; specific vitamins; steroids; industrial enzymes; fermented foods, and the like. The investment in modern biotechnology started in the early 90s. The first unit went into production on August 18, 1997, with the primary production of recombinant hepatitis B vaccine in genetically modified *Pichia pastoris* by Shantha Biotechnics Limited, an Indian biotechnology company headquartered in Hyderabad; Shantha was later acquired by Sanofi SA, France which is a French multinational pharmaceutical and healthcare company. After Shantha, several units have come up in India. The modern biotech products include recombinant hepatitis B surface antigen-based vaccines; granulocyte colony-stimulating factor; erythropoietin in various forms; interferon-alpha 2B and the pegylated product; epidermal growth factor; streptokinase; human insulin; a couple of other recombinant therapeutic proteins; and several monoclonal antibodies (m Abs).[2,3] Several companies are also producing multivalent vaccines, combining hepatitis-B surface antigens into them. Two monoclonal antibodies were invented in India; one of these, known as nimotuzumab, was India's first indigenously produced novel mAB and is indicated for treating head and neck cancer; the product was launched.[4] by Biocon, Bangalore, in 2006 with the trade name "BIOMAb EGFR"; a second one, itolizumab, also invented by Biocon, was approved for use in India in 2013 and was introduced by the company with the trade name "Alzumab." Alzumab is used for the treatment[5] of patients with active moderate to severe chronic plaque psoriasis. Many biopharmaceutical manufacturing units have been established in the country.[6]

INDIAN MODERN BIOPHARMACEUTICAL INDUSTRY IN THE GLOBAL CONTEXT

The global biopharmaceutical industry is making vibrant progress. There is, however, considerable variation in the estimate of the global biopharmaceutical market. One estimate.[7] places the market size at US$ 273.6 billion in 2022 and has projected to reach US$ 480.0 billion by 2028, manifesting a growth rate of 10.1% (CAGR) during 2023–2028. In another report,[8] the market size was US$328 billion in 2021, estimated to rise to US$ 853 billion by 2030 at a CAGR of 11.3%. A third report[9] projects the market size valued at US$ 350.53 million in 2021 and anticipates reaching US$ 639.26 million by 2029, with a CAGR of 7.8%. A fourth report[10] projects the market size at US$389.3 billion in 2021, reaching US$720.8 billion by 2030 with a CAGR of 7.1% during 2021–2030. A fifth report[11] places the market at US$ 407.72 billion by the end of 2023, expected to reach US$ 651.78 billion by the end of 2028 by registering a CAGR of 8.03%. According to the 5th Report, the market will be US$ 377.4 billion by 2022. The global market projection from these reports swings between approximately US$ 273.6 billion and US$ 407.72 billion, manifesting substantial variation. For this paper, the 2022 global biopharma market has been assumed to be US$ 340 billion, growing at 8% CAGR from 2022 to 2030. This estimate is an intelligent guess by the author. Biopharmaceutical products comprise various substances derived using recombinant deoxyribonucleic acid (rDNA) technology, including therapeutic and diagnostic proteins, vaccine antigens, orally used enzymes, monoclonal antibodies, cell and gene therapy products, xenotransplantation technologies, etc. The global biopharmaceutical market is a subset of the global total pharmaceutical market. The global pharmaceuticals market has been estimated[12] at US$1.48 trillion in 2022. In another estimate,[13] it was placed at US$1228.45 billion in 2020 and US$1250.24 billion in 2021. This paper considers the 2022 global market as US$1.48 trillion, growing at 6% CAGR. In 2022, the global biopharmaceutical market was approximately 14.8%, say 15% of the total pharmaceutical market.

Indian pharmaceuticals market size was reported[14] to be INR 1, 93,838 crores in 2022, growing at 7% annually in monetary terms. The 2022 market, converted into US$ by taking the exchange rate at INR 80 to one US$, worked out to US$24.23 billion. This figure reaches 1.64% of the global total pharmaceuticals market size of the same year (2022).

The author calculated the Indian biopharmaceutical market based on the sales turnover of 50 companies operating in India in biopharmaceuticals. Assuming that there are not more than 100 biopharmaceuticals company in the country, taking into consideration the actual sales figures in the published literature, and further thinking that the growth rate of biopharmaceuticals in India was not more than 10% annually in monetary terms, the calculated Indian biopharmaceutical market worked out to be INR 32261 crores during 2021–2022. The calculated figure was considered to be on the upper side of the estimate as the collected actual sales turnover of many companies included the total sales revenue, including biopharmaceuticals and non-biopharmaceuticals sales. Nevertheless, this figure for the Indian biopharmaceutical market was 16.64% say 17% of the total Indian pharmaceuticals market size, and is in close agreement with the relationship of the global biopharmaceutical market to the entire global pharmaceutical market. Therefore, the calculated figure of INR 32261 crores was considered as the upper side of the Indian biopharma market estimate during 2022. This figure converted into UD$ with the exchange of INR 80 to one US$ works out to US$ 4.032 billion and is approximately 1.14% of the total global biopharmaceuticals market. This is not surprising, having regard to the fact that Indian biopharma innovations are evolving. India is still in the learning phase, inventions in the biopharma sector are highly expensive, and the risks are very high. Consequently, enough private capital is not yet available for deployment for research. The government of India has allocated considerable sums for biotech innovations, but in the global context, the expenditure is considerably small.

In another recent study by the author on the discovery of novel active pharmaceutical ingredients (APIs), it was shown[15] that although India excelled in the manufacture of patent-expired generic APIs and formulations thereof and holds a leadership position in these subsectors, in the development of novel APIs, India continues to remain behind in innovations because of various reasons, of which lower R&D investment was a prime reason.

BIOPHARMACEUTICALS NEED SOPHISTICATED EQUIPMENT AND SPECIALIZED SKILLS: INDIA TO PRIORITIZE PRODUCTS AND SKILLS

Specific skills, instruments, and equipment usage patterns have significantly contributed to developing and manufacturing biopharmaceutical products, services, and technologies worldwide. The equipment, instruments, and abilities include microscopy and imaging; recombinant rDNA technology, recombinant products, and monoclonal antibodies, including the humanized products; proteins and nucleotide sequencing techniques and machines;

polymerase chain reaction (PCR) technology for the amplification of nucleotide sequences; chromatography; gel electrophoresis; LC-MS and MALDI-TOF for molecular weight determinations; protein-based and DNA-based chips and microarrays; flow cytometry for cell sorting; other cell sorting techniques; bioinformatics; air handling, decontamination, and sterilization (space, equipment, materials, and air) capabilities; besides others.

After the discovery of rDNA technologies, followed by the advent of genomics, proteomics, and multiple other omic technologies, along with improvement in fast conduct of nucleotide sequencing of divergent cells and life forms plus capacities to modify the natural genomic sequences of living entities (genome editing technologies and synthetic biology expertise), human abilities to develop and produce living organisms of improved genetic traits increased exponentially. Multiple technological inputs emanating from bioinformatics; fast computation technologies; development of algorithms and artificial intelligence (AI); skills in multiplying human, animal and insect cells in bioreactors in high cell density conditions; skills in handling dangerous micro and nano-sized life forms in safe manufacturing facilities (biosafety level [BSL] or pathogen/protection level 2, 3, and 4 facilities); skills in separating active biochemical substances by designing and using ultracentrifuges, membranes of various qualities, and sophisticated chromatographic systems; capabilities to protect vulnerable biological materials in nano-containers; constructing sophisticated machinery for freeze-drying of thermo sensitive materials under sterile conditions; skills in fast analyzing and determining the structures of chemical substances; improvement in analytical and instrumentation techniques; and several other such modern techniques revolutionized human capacities to handle and use biological materials and resources in much more efficient ways, minimizing risks, and in many cases requiring lesser energies and discharging lesser greenhouse gasses in various parts of the world.

Intense persuasion for skill development in biopharmaceutical technologies outside India during the last few decades has resulted in the invention of novel techniques, instruments, and skills utilized in developing unknown biopharmaceutical substances. Such skills were invented and initially created outside India. Indian scientists, academia, and industry have used these skills in different aspects of biopharmaceutical product development and management at a later stage. These skills are linked to using exact instruments and novel substances that India had to procure at high prices.

Nevertheless, many Indian professionals trained in various aspects of biopharmaceutical technologies abroad have returned to India and have got engaged in furthering their work in Indian institutions and industry, and have taught many local people, who have then engaged themselves for further development of their skills. In the meantime, the Indian government had set up several institutions where, within the country, these skills could be used for furthering knowledge and expertise. Such skillful people and the instruments are the strengths on which the Indian biopharmaceutical industry is being developed and expanded. The government has also allocated sizable sums for R&D. Utilizing a combination of these skills and resources, the Indian industry is producing a host of modern biotech diagnostic devices and therapeutic substances, as mentioned. Collaborations with knowledge-based foreign companies, institutions, and agencies have also eased the process. In the meantime, several new innovative products have entered the market from foreign companies, and more new products must be added to the Indian products basket too.

Building expertise in cloning certain cell types is essential in developing recombinant deoxyribonucleic acid (rDNA) products. Most presently used products deploy specific types of *Escherichia coli*, *Saccharomyces cerevisiae*, *P. pastoris*, *Hansenula polymorpha*, and Chinese hamster ovary (CHO) cells lines. In a few cases, BHK and VERO cell lines have been used. Only one product in India has been produced in baculovirus-mediated insect cell lines. The industry will do well if it narrows its choice to specific, well-defined, well-characterized, and well-organized *E.coli, P.pastoris,* and CHO cell line-based products. More than 60% of the therapeutic modern biotech products are made in CHO cell lines. Operations are another important area where the right choice of processes must be made. Since the volumes are small, using glass or SS reactors for cell multiplication can be an alternate option. If CHO cell lines are the main workhorses, it is beneficial to look for disposable bioreactors to cut down the cost of sterilization, which is sizable. Chromatography is a downstream processing operation where standardization is required to minimize the use of columns; rugged columns must be used that can be resorted to cleaning in place (CIP). Formulation development is another area where success would depend upon simplification and using simple, easily sterilizable substances.

Tissue target-specific deliveries requiring biodegradable polymers and nanoparticles are other areas where high technologies can be developed, and the industry can be set up.

Single-cell imaging, sequencing, and analysis enable the study of cellular heterogeneity comprehensively within a 'homogeneous' stem cell, including autologous as well as allogeneic stem cells as also other ' homogeneous' differentiated cells such as mesenchymal, epithelial and muscle satellite stem cells and other differentiated cell population. Single-cell analysis is the only choice to study physiological functions in adults and embryos. Single-cell analysis results can assist in studying drug development and understanding certain chronic diseases more distinctly. It also helps develop regenerative medicines, including autologous and allogenic cell therapy, gene therapy, tissue engineering, and multiple other wound-healing application areas.

Stem cell research has picked speed, and products are on the horizon. One aspect of the activities is to isolate and preserve the embryonic stem cells. This work has made considerable progress with the hope that methods shall soon be in place to multiply them in the desired direction for differentiation. However, the meat is in the ability to develop the re-programming techniques to induce pluripotency in ancient genomes. Such work requires the development of retro and non-retroviral means of overexpression of specific oncogenes into engineered cell types. Non-retroviral means would be preferred as the retroviral means change the chromosomes considerably by inserting viral DNA into them, which is not preferred.

Among the new biopharmaceutical products under development, m RNA-based therapies are making fast inroads into human therapy. The two m RNA-based COVID-19 vaccines of Pfizer and Moderna were the first line products, and many other m RNA-based products for use in other therapy areas to treat chronic diseases, including cancer, chronic obstructive pulmonary diseases, and arthritis shall evolve soon in the international market. India made some progress in developing m RNA based SARS-Co V-2 vaccine. Gennova Biopharmaceuticals, Pune, developed[16] an mRNA COVID-19 vaccine, which is available as GEMCOVAC-19. A research team at the Atal Incubation Centre of the CSIR-Centre for Cellular and Molecular Biology (CCMB), Hyderabad, is developing[17] a candidate m RNA vaccine against SARS-CoV-2. More developments are anticipated in m RNA-based therapies from India. One essence of m RNA-based products is in the skills for developing highly monodispersed nanoparticles of precise size range below 50 nm in diameter. Micelles and reverse micelles techniques can make it.[18] Access to specialized amphiphilic substances of lower toxicity is another crucial requirement.

In-vitro-modified somatic cell-based therapies are also developing fast. Certain types of somatic cell-based gene therapies are approved in certain countries to treat genetic disorders, such as Leber congenital amaurosis, melanoma, spinal muscular atrophy, certain blood diseases, etc. Germline cell and embryo genome editing are currently illegal. No country yet permits heritable human genome editing as a therapy except China and the United Kingdom, where human germline genome editing is allowed for certain types of work.[19] Although heritable human genome editing is the subject of intense debate worldwide because of its possible consequences for offspring, research on this technology is vibrant in many countries, including India. India has its Institute for Stem Cell Science and Regenerative Medicine, Bangalore, where research is conducted to study different aspects of stem cells and regenerative biology, emphasizing translational outcomes.[20]

Genome editing technologies enable scientists to change an organism's DNA, thereby enabling the modification of the genetic materials(addition, deletion, and revision) at particular locations in the genome, making fast inroads; these technologies hold the promise of inventing new ways of treatment. Use of techniques emanating from Zinc finger nucleases (ZFNs) techniques, transcription-activator-like effector nucleases (TALEN) techniques, and the clustered regularly interspaced short palindromic repeats (CRISPR/Cas9) system are used for genome editing technologies. Chimeric antigen receptor T-cell therapy (CAR T-cell therapy), where T-cells of patients suffering from certain types of cancer are modified genetically and multiplied in-*vitro* and resent the modified pool of T-cells into the donors are already in use elsewhere. In all these areas, Indian developments in terms of translational outcomes are yet at the research stage.

Another area is also worth mentioning. A large number of people die the world over from vital organ failures. Some of such unfortunate could be saved if they could be transplanted with organs from the rightful donors. Finding a donor who can provide the biologically matching proper organ is difficult. There is a shortage of human organs required for transplantation purposes all over the world. India has its Transplantation of Human Organs Act (THOA) 1994, which was enacted for using human organs for therapeutic purposes, and which was amended to form the Transplantation of Human Organs (Amendment) Act 2011, and subsequently, the Rules, known as the Transplantation of Human Organs and Tissues Rules[21] 2014. But the shortage of human organs continues to stay. An alternative is consequently needed, and xenotransplantation technology is essential.

Scientists have developed methods for developing humanized organs in animals; such organs match immunologically very closely to the human system. To check in size also, it has been found that the organs of certain animals like pigs could closely fit the size requirements. Combining these factors, efforts are being made to develop genetically modified humanized pigs for the use of the organs of animals in humans. Such technologies are within the preview of Xenotransplantation, a procedure[22] involving the transplantation, implantation, or infusion of live cells, tissues, or organs from a nonhuman animal source into the human body. Much research on these issues is being carried out[23,24] outside the country. This being an important area of biopharmaceutical product development, this area should be pursued vigorously in the country.

India has not yet have an effective action plan for developing humanized transgenic animals. However, the Government of India supports programs[25] for developing transgenic animals. Including programs for creating specific types of humanized transgenic animals would speed up drug development against certain deadly diseases.

Because of remarkable improvements in computational power coupled with advancements in AI technology, the feasible ways AI can improve the efficiency of the drug discovery and development process has been reviewed. It has been concluded that although, at present, no new or improved drug has yet been invented, through AI approaches, the potential[26] of doing so quite faster is high. The use of AI in the pharmaceutical industry has been highlighted,[27] where the development of pharmaceutical products from the bench to the bedside can be more intelligently guessed through AI, and AI would assist positively in decision-making for rational drug design; AI may also help in the clinical data generation process. AI is anticipated to speed up the time required for new products with better safety and efficacy profiles to come to the market. Consequently, there is a constant interest from multinational giants in using AI in the pharmaceutical industry, and huge investments are being contemplated.[28] Biopharmaceutical engineers and technologists are making fast progress in designing proteins[29] that never existed in nature, but that could be created and used for making a therapeutic intervention that was not even conceivable earlier. This is possible through advanced machine learning techniques and AI-based computational tools. AlphaFold 2 is an algorithm[30] used for quickly predicting protein structure from the data of amino acids sequence of proteins and peptides. There is a long list of machine learning algorithms,[31] and AI-assisted design of therapeutic proteins is blossoming fast. The use of AI in the biopharmaceutical industry shall positively contribute to its developmental goals. India must take a fast-track initiative in developing the area to benefit the biopharmaceutical industry.

Regarding biotechnological skills in the Indian industry, the level is yet up to the handling of the mammalian cell stage. There are some pockets where skills for handling high-risk substances are in place. However, the Indian industry is slow and has to go a long way to catch up with the global level's highly sophisticated skills and proficiency levels. The reasons are not difficult to find. The development of a bio-pharmaceutical product is highly capital-intensive. Studies have been made to ascertain the costs of developing small drug molecules, and the costs from concept to marketing have been estimated through several publications. It is estimated[15] that US $ 1.2 to 1.4 billion are being spent to have a jackpot pharmaceutical product.

Therefore, more investment is required in India for research and development. A white policy paper on the globally emerging novel biopharmaceutical technologies and Indian plans for making a long-term impact on such emerging biotechnologies need to be prepared with a long-term action plan for enabling India to benefit from their development in the country.

INDUSTRIAL ENVIRONMENT

There are considerable shortages of skilled leaders to run the sophisticated biopharmaceutical industry to meet the present commerce needs. Biopharmaceutical industries belong to the high-tech sector; therefore, the leaders must have adequate managerial skills and expertise in modern biotechnology, including research and production. The competitive global environment requires leaders to have front-line knowledge of manufactured or planned products. This responsibility demands knowledge about the market, the whole scenario of existing products, the existing costs and the means of cost-saving, the information about the new products pipeline, the ability to appreciate the line of R&D being pursued or to be followed in the company (which has to be application-oriented), the capability also to judge people who would be conducting R&D, the ability to effectively communicate so that the team is motivated to the pre-set goals for production, research, and development. Since biopharmaceutical products are tightly regulated during the developmental and application stages, leaders must undergo continuous training to update their knowledge to remain current.

The industry has constraints of abundant infrastructure, finance, and capabilities. Access to published research

literature from established journals is limited, as a sizable part of the industry does not consider it essential to subscribe to state-of-the-art journals on the ground of saving costs. There is no strong culture of reading to remain current on science and technological issues. The leaders must make a mark within the available facilities or source access to these resources to improve their performance. Conducting seminars regularly with extensive employee participation would promote reading habits. Multi-tasking exposure and experience are essential.

The industrial environment is not yet strong to maintain adequate levels of confidentiality, and the issues of IPR are more public-friendly; leaders have to take these into account and try to be ahead of the existing knowledge with adequate mechanisms for IPR protection.

The production and the research infrastructure in the industry are often not adequately evaluated either by the owners or by the regulatory authorities to ascertain if the facilities and the people are adequate for the tasks that are being handled by it. The list of expensive equipment in place or the number of 'qualified people" people recruited is not the end of the evaluation about whether the facility is reliable for quality production or whether the R&D team can deliver. Objective judgments must be applied, and collaborations with expert institutions should be done where feasible.

The use of AI in the Indian biopharmaceutical industry needs to be flagged, primarily in organizations engaged in developing and manufacturing protein-based therapeutic substances.

Another shortcoming is that the Indian biopharmaceutical industry is not adequately linked with R&D institutions, so the basic knowledge flow is slow. The statutory requirements are often more demanding, and the confirmation criteria for the approval process under the statute are sometimes hazy for new products to be introduced. The opinion-makers are often biased and stick to borrowed opinions from outside the country. Industry managers must consider multiple factors and evolve strategies to move quickly within the existing environment.

All these situations must be critically examined, and better solutions should emerge to improve the industrial environment and benefit the country.

JAN AUSHADHI CAMPAIGN

India is ahead of many countries in fulfilling important social objectives in providing essential medicines at affordable prices to the people who make their own out–of–pocket expenses on medicines. The government of India launched[32] the Pradhan Mantri Bhartiya Janaushadhi Pariyojana (PMBJP) in November 2008 to make quality, non-branded generic drugs available at affordable prices.

Much before the launch of PMBJP, for the first time in India, in the Report[33] of the Committee on Drugs and Pharmaceutical Industry, popularly known as the Hathi Committee Report, brought out in 1975, there was detailed study and recommendations on the introduction on pharmaceutical formulations in non-branded generic name in the market to introduce quality formulations of different medicines at affordable prices. Indian drug prices control policies and orders, promulgated after 1975, emphasized promoting the sale of generic formulations with lesser excise duties than the corresponding branded formulations. However, the sale of generic formulations could not make much material change in terms of increased sales of generic formulations. During 1978-'79 and 1979-'80, generic medicines in India constituted approximately 1.7% and 1.9% of the total trade sale of pharmaceutical formulations.[34] It was suggested that besides the research-based formulations (protected by intellectual property rights or by secrecy), the formulations manufactured and marketed by the companies in India be encouraged to be introduced in generic names with policy supports. Indian pharmaceutical policies[35] over the years, though leaned towards encouraging the introduction of formulations in generic names, could not promote the fast introduction of non-branded generic formulations in the Indian market. However, there has been phenomenal growth in the opening of branded-generic formulations. A significant share of non-branded generic medicines appears to be from the 'Pradhan Mantri Bhartiya Janaushadhi Kendra (PMBJK) outlets. A recent report stated vast differences between and among the prices of branded-generic formulations and non-branded generic formulations.[36] The sales turnover of medicines sold through PMBJK outlets was INR 893.56 crores (the financial year 2021–2022), and it was stated that the sale of these medicines enabled a saving of approximately INR Rs. 5300 Cr. to the citizens.[37] These figures were approximately INR6193.56 crores or US$ 0.774 billion, approximately 3.2% of the total Indian pharmaceutical turnover. This shows that the sale of non-branded generic pharmaceuticals still has a low share of the total pharmaceuticals turnover, though it may be rising slowly. In the Indian context, the sale of pharmaceutical formulations is still preferred in brand names by the Indian Pharmaceuticals Industry.

The global sale of non-branded generic pharmaceutical formulations sale started rising in various developed countries, starting from the USA, after the USA had enacted

"The Drug Price Competition and Patent Term Restoration Act" on 24th September 1984, which resulted in the rise in the prescription writing during the recent time, by the medical practitioners to nearly 90% in generic names. For more than 80% of approved pharmaceuticals, generic versions were available[38] in the market.

India started promoting[39] the sale of generic formulations by initiating its program "Jan Aushadi" (translated as "Medicines for People") on 25th November 2008, and up to the present time, the program is gradually getting intensified. After the launching of PMBJP, the Pharmaceuticals & Medical Devices Bureau of India (PMBI) was established by the government with the support of all the central public sector undertakings (CPSUs) engaged in the manufacture of drugs and pharmaceuticals for fructifying the manufacture, distribution, and sale of generic formulations across the country. PMBI is the implementing wing of PMBJP. The PMBJP campaign was launched by the Department of Pharmaceuticals with Central Pharma Public Sector Undertakings through dedicated outlets called 'Pradhan Mantri Bhartiya Janaushadhi Kendra (PMBJK). At present more than 8600 numbers of PMBJKs are functional across the country. The Product basket of PMBJP comprises 1759 drugs and 280 surgical products. The contributions of biopharma are not separately reported. Certain biopharmaceutical products, such as digestive enzyme preparation, corticosteroids, sterile insulin preparations, sterile erythropoietin injection, etc., are also available from PMBJP outfits. More biotech medicines are anticipated to be included in large portions. Biopharma products continue to remain expensive in the private open market.

The PMBJP campaign is essentially a social program; such a program can be successful if the PMBJKs are profitable, as these establishments are run mainly by private people. Intense sale from such PMBJKs is one condition for ensuring profitability; the operators receive a 16% commission on the MRPs. In many cities, the PMBJKs are running successfully. To improve the public health of people, PMBJB is considered a vital right step taken by the government for the people. However, it might need to provide considerable subsidies to the manufacturing CPSUs to keep up the tempo and to attract competent people to manage it.

RESEARCH AND DEVELOPMENT EXPENDITURE ISSUES

Developing countries all over the world, including India, China, certain other South Asian countries, Brazil, and some other South American countries, including some Caribbean countries, are trying hard to catch up with the developed world by narrowing the gap over time, between the expenditure incurred by the developed world in R&D compared to those spent by the developing world. The total R&D investment in the world during 2000–01 was estimated to be 740.78 billion PPP $, which increased to 2,192.38 billion PPP $ during 2017–18. Of the total R&D expenditure of 2000-01, the developed world spent about 82% and the rest 18% was spent by the developing world. But in 2017-18, the global percent share of the developed world dropped to 59% of the total, and the expenditure of the developing world increased to 41% share. These figures indicate that the developing world is investing more in inventions and innovations. The R&D expenses are estimated in PPP $, which refers to the value in U.S. dollars using purchasing power parity conversion factors instead of market exchange rates. Indian R&D expenditure was about 0.7% of its GDP in 2017, and in monetary terms, it was approximately 63.2 billion PPP $, which was only 2.9% of the global share of R&D expenditure during the year. Indian Government committed expenditure[40] on extramural R&D projects in biological sciences during 2016-'17 was INR 498.56 crores (20.3% of the total extramural R&D projects), which was 207.75 million PPP $ only. The biotechnology industry during the year consisted of one public sector undertaking with an annual R&D expenditure of INR 9 lacs only and 163 private sector units whose annual R&D expenditure was INR 1071.3 crores (446.4 million PPP $ only). The 163 private sector biotechnology industry includes all the biotechnology subsectors, including the biopharmaceutical subsectors. The combined R&D expenditure (private sector plus Government committed R&D in biological sciences) was only about 654.15 million PPP $. Compared to this, only the publicly traded global biotech companies spent[41] about 32.93 billion US$ in 2017; the total R&D expenditure of all the global biotech companies would be much more significant. Even compared to the R&D expenditure of the publicly traded global biotech companies, Indian R&D expenditure in biological sciences was way behind the worldwide expenditure on R&D. Therefore, unless the Indian government expenditure in R&D is increased sizably, and unless the private biotech sector is encouraged to invest in biological sciences heavily, it would be a peril to catch up the world developments, and India would continue to be behind in innovative new biopharmaceutical products; such products would be appearing in Indian markets from Indian innovations, several years after these are sold by the IPR protected innovators residing in the developed countries.

CONCLUSION

The scenario of the biopharmaceutical industry in India is complex and multifarious. Although there shall be a

considerable increase in the production of conventional biotech products in the healthcare area, including sera and vaccines, diagnostic devices, and certain fermentation-based therapeutic substances, the modern biotech products deploying recombinant DNA technology shall hover around patent expired therapeutics and diagnostics. Government support, especially in providing seed capital, encourages the expansion of new industries in the small and medium-scale sectors. "Cost-effective Innovation" is becoming the backbone of progress in manufacturing patent-expired products.

Societal demand shall encourage the registration of high-tech new products, the technologies of which are developed outside India. Such products shall be expensive, and it would not be easy for an ordinary person to afford them until they are IPR protected. Therefore, cheaper substitutes must be in place. As the reimbursement of medical treatment costs is not liberal and adequate for the ordinary person, the situation is likely to contribute to societal turbulence. The government's PMBJP attempts to bridge the gap between the demand and affordability of many medicines, including life-saving biopharmaceutical products. The product range must expand, and appropriate policy initiatives and action plans must be developed quickly.

For developing a jackpot of new biopharmaceutical products, the Indian environment is far from ideal. Deficiencies can be bridged if determined steps are taken, requiring allocating more money and spelling out innovative policies for conducting research in strategic areas in a PPP manner with a strong emphasis on IPR protection and encouraging foreign collaboration on a liberal basis. A white paper needs to be prepared so that the country is aware of the direction it is making moves on a solid footing of law and intellectual security.

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Conflicts of interest

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