Review Article

Novel active pharmaceutical ingredients from India: The issues—Part-II

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Abstract

India has made a mark by discovering at least 16 novel synthetic active pharmaceutical ingredients (APIs). However, this number is quite small when compared with the number of APIs invented the world over in the allopathic system of medicines, the numbers of which according to the estimate of the author stand at more than 5000, of which presently nearly 3000 numbers are in therapeutic use against human diseases/ailments. In India, nearly 2200 numbers of these APIs are presently in use. India has made a mark in the supply of branded generic and generic formulations for use in the country and abroad in an environment of cut-throat competition. To maintain and improve the mark, India needs to carry out R&D not only for process innovation but would also have to invest and invent novel APIs. The analysis shows that the present investment in R&D and the policies followed for promoting research for new drug development are not adequate for the country to be dominant global player. Suggestions have been made to improve the present situation.

Keywords: APIs invented from India, Indian pharmaceutical industry, novel active pharmaceutical ingredients

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INTRODUCTION

India had presently established a sound and proficient pharmaceutical industry with more than 3,000 pharmaceutical companies which are engaged in the manufacture of about 60,000 brands of formulations using nearly 2,200 generic active pharmaceutical ingredients (APIs). About 1000 generic APIs are locally manufactured, whereas about 1200 are imported and used. India has maintained its mark as a supplier of quality medicines to cater the needs of India as well as to serve the world in the areas of generic formulations where there is intense and cut-throat market competition. Moreover, India heavily depends on the supply of a large number of generic APIs and multiple numbers of raw materials from imported sources to keep its local manufacturing of certain crucial generic APIs operational. To maintain its present global status, India needs to continuously innovate to remain cost-competitive. But to excel beyond its present status, India must venture into the discovery of novel APIs.

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THE INTENT OF THE PAPER

The paper intends to focus on the policies that are to be in place to enable India to move toward the discovery of new chemical entities (NCEs) and novel APIs therefrom. This

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area requires massive R&D investment. Indian research in this area is yet quite selective, and only a few companies have invested in this area of pharmaceutical research. The novel drugs manufactured by deploying rDNA technology have not been included in this review.

METHODOLOGY OF THE STUDY AND EXPERIENCE OF THE AUTHOR

While conducting the study, information was gathered from the websites of all Indian institutes and universities as also from the multiple pages existing on the internet. Google search engine was used. The websites of more than 40 API manufacturing units were also consulted to obtain information. Also, the websites of the Indian government departments involved in the administrative function, promotion, R&D support, and funding of research on drugs and pharmaceuticals were consulted. The author has a background of hands-on experience in research and development, production and administration of drugs and pharmaceuticals, diagnostics, and clinical chemistry reagents for several decades.

THE WIDE-RANGING ISSUES

APIs discovered in India

India has thus far discovered 16 numbers of novel APIs which include Urea stibamine; Methaqualone; Enfenamic acid; Hamycin; Centimizone; Centbutindole; Ormeloxifene; Centpropazine; Centbucridine; alpha, beta-Arteether; Bulaquine; Candocuronium iodide (INN, formerly known as Chandonium Iodide, HS-310); Nitroxazepine (brand name Sintamil); Amoscanate (INN, also known as nithiocyamine); Saroglitazar (INN, rade name Lipaglyn); and Diperoxochloric Acid (tradename of formulation WOXheal). The discovery of the number of novel APIs is no doubt a remarkable achievement for India. These emanated from the strong commitment and devotion of a small number of outstanding scientists who played a key role to discover and invent. Inventors are a separate class of people who are to be incessantly encouraged to remain focussed on their tasks by providing all the necessary amenities and supports. Their efforts bear fruits when they receive all-around supports. The path of the invention is extremely lonely. Inventors walk lonely often encountering failures and frustrations. Their thought processes are enshrouded within themselves. They talk to themselves and find newer pathways from within. Their journey is ardent. It is to be recapitulated in this context that the paths for novel API discovery have undergone a sea change over the years. The path has taken a multidisciplinary approach and is linked with intense knowledge in chemical synthesis, medicinal chemistry, combinatorial chemistry, high-throughput screening techniques, molecular biology, protein crystallography, computational chemistry, knowledge of physiological mechanisms of disease, and many more. Novel API discovery approach often starts from a rationally argued hypothesis to design NCEs, proceeds through multiple mechanistic approaches, and makes a start. To reach the end with a successful novel API requires the involvement of multiple actors. It is no more possible to invent or discover a novel API on a single-handed approach and using traditional techniques of drug discovery.

For a country of Indian magnitude, the number of novel APIs discovered is indeed very small. This would imply that there was not much enabling multidisciplinary infrastructure, funding support, enabling regulatory bodies, political will, and societal encouragement for cracking a disease problem. Moreover, the inventors could not adequately reap the benefits of their discovery in terms of societal recognition or amassing wealth. Very few actors had therefore devoted their career to the discovery of novel APIs.

Business environment for manufacturing generic APIs, progresses and skills

In contrast, India made phenomenal progress in innovation in the whole area of production of cost-effective generic APIs and pharmaceutical formulations manufactured therefrom. The reasons for these are many. First, the grounds for incremental innovation were established by the political will and the government intentions as were reflected from the time of Indian independence, essentially through Indian Public sector efforts earlier and later through India private sector, strongly promoting efforts of import substitution. The political will and the government intentions changed from 1991 after India resorted to an open market economy; while the Indian government efforts were to enable the country to be an effective global player, the main constituent of dominating innovative economy, which depends on highly productive new API technologies, was not adequately geared up nor enough money could be found for such purposes. However, because a strong culture of innovation was already built in the country, the Indian private sector swung into action and produced cost-effective innovative processes for producing generic APIs of diverse kinds in multiple therapeutic areas. In this context, it must be recalled that no stone was unturned to procure cheaper raw materials by the Indian private sector to procure drug intermediates from cheaper sources within the provisions of the law to turn out cost-effective generic APIs for sale within and outside the country. The Indian talented individuals in chemical synthesis, in the handling unit processes, and the unit operations for the manufacture of generic APIs have found their jobs in multiple numbers of

R&D as well as manufacturing operations in the country. They have been and are being reasonably compensated for their talents in terms of salary and remunerations by the successful private entrepreneurs and manufacturers of APIs in the country. Such talents have preferred private jobs to jobs in the Indian public sector undertakings because of more monetary gains and monetary satisfaction. Innovations brought about by the talented Indian skills were the main reasons for India's becoming a forerunner in the manufacture of generic APIs and formulations thereof more cost-effectively. Indian API manufacturers had also generously imported raw materials and drug intermediates, especially from China as these were available at cost-effective economic prices but could turn out finished generic APIs that were not only of the right quality but also their production was carried out, deploying more cost-effective technologies. In this process, India could produce and export about 600 generic APIs out of some 1000 generic APIs manufactured locally. Indian entrepreneurs need also to be applauded for the outstanding success. Earlier, India was manufacturing much larger numbers of generic APIs locally when the industry received price-protection for the local manufacture and sale of generic APIs; many units could not sustain the global competition after India decided to open up its economy in July 1991 and later joined the World Trade Organization from 1st January 1995.

It is to be emphasized in this context that since the independence of India, the multiple policy incentives promulgated by the Indian government were primarily to put efforts toward developing alternate processes for already existing APIs. The attention and emphasis on the development of NCEs for use as novel APIs were meager, primarily due to inadequate availability of research infrastructure and inadequate deployment of resources and trained manpower for such purposes. Further, there was the imposition of price controls and later the introduction of a dual-pricing system for active pharmaceutical substances. These policies not only hindered the progress in the development of new APIs but also took away the incentives for improving process efficiency, deployed in the manufacture of known APIs. The policies adopted also resulted in the reduction of profit margins substantially, and there were not enough surpluses left for allocation for major developmental efforts or even basic research. Efforts of conducting basic research by certain transnational companies, which started in the 1970s and 1980s, and to have complete freedom in selling their research products at their free wishes were denied; consequently, these companies closed down their basic research facilities throughout the country. Moreover, basic research in synthesis for the development of novel APIs was found to be lesser productive in terms of attainment of success and called upon drawl and usage of excessive resources. Basic research required a liberal support mechanism to the establishments supporting it. Indian pricing policies were not conducive to supporting the establishments for generating surpluses without restrictive conditions. Failing to appreciate the need for generating adequate surpluses for those pursuing basic research resulted in gradual shying away from such endeavor. India was slow in modifying its industrial- and trade-related policies to remain competitive in the international arena. There was a strong reliance on public sector initiatives, especially in the late 1960s, 1970s, and beyond. The result was the induction of insurmountable inefficiencies in basic R&D operations. As a consequence, the basic production of APIs became more expensive than international prices. India managed to remain competitive in the manufacture and sale of pharmaceutical formulations, especially through stringent price control mechanisms, although the incentives for the conduct of basic research for the development of new APIs dried up. From the time of independence up to the late 1980s, policies enumerated by the government placed major emphasis on creating initiatives that had worked toward an equitable distribution of wealth amongst its people. These policies did their best up to the late 1980s but later started showing symptoms of weakening. Indian pharmaceutical industry started showing symptoms of weakening the Indian economy. Wherever there were avenues for imports, the Indian producers of pharmaceuticals procured cheaper imports through others that were often non-producers but were only traders. By the late 1980s and early 1990s, it became evident that the policies needed to be revised. The World Trade Organization (WTO) policies were in vogue at this time, and India became a member of the Treaty in April 1994. In the meantime, the liberalization policy was announced in July 1991 by the Indian government allowing global trade on equal label-playing conditions, which would gradually provide equal opportunities for all businesses and all sectors, which were involved in the country's economic development. India has always believed that all of its citizens should receive equitable opportunities to allow the poorer class to reap the economic benefits along with the rich. Therefore, from the late 1940s up to the late 1980s, policies created by the government placed major emphasis on creating initiatives that have worked toward the rationalization of equitable distribution of wealth.

Entrepreneurs create wealth. Entrepreneurs are exceptionally intelligent people. They create wealth by deploying capital, labor, and technology. Wealth created by the entrepreneurs remains with them if adequate interventions are not exercised by the political system and by governments. India's adoption of socialistic patterns of policies enabled it to improve its economy considerably; however, putting barriers to entrepreneurs toward amassing surplus wealth generated by them by adopting socialistic

patterns of policies created disincentives to multiple able entrepreneurs. The negative impact was perceived as too small for a long time and India continued to rule with its socialistic policies until the late 1980s. In the meantime, the adoption of such policies bred the rise in corruption. Further, in the pharmaceutical industry, in particular, creation of industries with manufacturing capacities dispersed regionally without attention to the economy of scale, the limited scope of further expansion of manufacturing capacities, price protection of APIs to enable industries to recover "cost-plus" margins from a non-competitive local (Indian) market place, and that any additional initiatives favorable for the public or local industry to promote economic welfare could not last beyond the late 1980s. The policies existing at that time, in turn, caused reserves of foreign exchange to become lower and nearly created insolvency in the economy, resulting primarily in inefficiencies from productivity in most of the API-producing pharmaceutical industries but particularly in the public sector undertakings. Consequently, a need arose to correct the situation. As a result, the Central Government modified the previous developmental policies from the early 1990s. The licensing policy was enormously liberalized through the enactment of simpler policies successively over the years through policies by the Foreign Investment Promotion Board of the Union Ministry of Industry to attract large foreign investments and more efficient technologies. It is anticipated that the present policies, conducive to the current global economic policies, would enable to partly correct the situation gradually over some time. However, much more resources in a directed manner in mission-mode approach have to be diverted to enable India to emerge as a leading country to the development of novel APIs. Additional newer policies are called for to enable more resources to be inducted and diverted toward attaining such goals. Some framework of activities and directions has been suggested.

It needs to be mentioned in this context that India has developed strong capabilities and skills in chemical synthesis operating at the manufacturing plant level, which requires in-depth knowledge in various complex synthetic methods such as Aldol condensation, Allan–Robinson reaction, asymmetric reactions and reductions, aliphatic and aromatic nucleophilic substitution, Bechamp reduction, Beckman rearrangement, Birch reduction, Blanc reaction, catalytic hydrogenation, catalytic reduction, Claisen condensation, Clemmensen reduction, cyanation and handling of inorganic cyanides, carboxylation, cryogenics, enzymatic reaction, Dies–Alder condensation, Friedel–Craft alkylation and arylation, O-alkylation, N-alkylation, Grignard reaction, halogenation, Hofmann degradation, hydroboration and organoborane reactions, Meerwein–Pondorf–Valery reduction, Moffatt–Swern oxidation, organometallic reactions, and many more, including handling of hazardous reagents used in non-aqueous environment and sometimes working at ultralow temperatures. The points to be highlighted are that Indian capabilities exist for handling such reactions on the pilot and industrial scale, which require years' efforts and practices. These skills shall go a long way in developing cost-effective processes for new APIs whenever developed in the country. Indian generic API industry is highly organized, and it is growing at the rate of about 10% per annum in value terms.

It is believed by the author that the Indian emphasis of import-substitution research widely acclaimed to be a success story has reached its saturation level. India must come out of this "me too" syndrome if it wishes to be a strong global player in the discovery research of novel APIs. There is a wide belief that pharmaceutical research is cheaper in India; it may be cheaper if the country hovers around import-substitution research. It is not much cheaper if properly compared for novel jackpot drugs that have been successful in the internal arena. Accepting this logic would mean much more diversion of resources for novel API discovery research. One main reason why India could not come out with any novel API of jackpot value is that there never were adequate resources and establishment of special teams for cracking a problem of international magnitude. Another reason was that the Intellectual Property Rights (IPR) of inventions could not be ruthlessly protected. There was a need for amending the provisions of IPR prevailing before the 1970s for a certain time, and this policy has promoted the country to reach global heights in generic drug manufacture and sale. However, after 1991 when India decided to open up, the decision was not strongly stewarded by the country, neither by showing a strong political will nor did the Indian industry, except a handful of them, had shown leadership by walking differently for novel invention. Those actors that walked to invent could not become successful in turning out any jackpot category of new drugs. The main reason again was the inadequate availability of more resources. There are many other reasons too, which are not discussed here. It became increasingly clear that novel API discovery was not easy.

India is still engaged in novel drug discovery research in multiple of its institutions, especially the government-funded institutions, using traditional methods of drug discovery approach. Traditional drug discovery techniques involving the search for active ingredients in and from natural sources; random screening of chemicals produced by chemical synthesis; trial and error method using

multiple new synthetic products or products isolated from natural sources; accidental discovery; and even the ethnopharmacological approach based on integration and utilization of several disciplines such as chemistry, botany, and pharmacology, etc. which were used earlier as techniques for new drug discovery are approaches that are considered myopic in the present-day competitive environment of new drug development research. In the phenotypic drug discovery approach which is comparatively newer and which is also described as the classical pharmacology approach, the investigators rely on phenotypic screening of synthetic small molecules, natural products, or extracts on intact cells or whole organisms to identify substances that have a desirable therapeutic effect. By such screening techniques, using the knowledge of medicinal chemistry, multiple hit-compounds have been found by many investigators the world over, and from these after optimization of desired properties, several novel APIs have come out. The use of this technique requires a dedicated and intelligent team with multiple skills. Saroglitazar was discovered in India by using the phenotypic drug discovery approach. All the other new drugs discovered in India were by using traditional drug discovery techniques. The author is of the view that India needs to come out from such traditional approaches and move forward by extensively deploying the modern approaches.

Assessment of discoveries made in India in novel APIs from 1994 up to mid-2016

In a survey carried out on the Indian companies between the period 1994 and mid-2016 on proprietary drug discovery and development efforts,[1] mention was made of only one novel API coming from India. This was from Zydus Cadila Group (Cadila Healthcare), which was Saroglitazar, an antidiabetic drug. It was further mentioned that there were only slightly over 80 novel NCEs emerging from Indian companies. The relatively small numbers of NCEs identified from Indian companies during this long period were indicative of India being far behind from becoming a dominant player in novel API discovery in the global context. During the time of writing this paper in January 2021, only one additional novel API by the name Diperioxochloric acid and its formulation entered into the Indian market. The novel product was co-developed through a collaboration between Centaur, Mumbai and Cyto Tools AG, Germany. Centaur Pharmaceuticals Private[2] Ltd (Centaur), Mumbai entered into collaboration about 15 years ago, with CytoTools AG, Germany to co-develop a promising new molecule by the name Diperoxochloric acid (DPOCL), which belonged to CytoTools. The molecule was for the treatment of diabetic foot ulcer, and the formulation of the molecule was being marketed under the trade name "WOX heal."

Evolution of new techniques in R&D pathways for novel drug discovery

In earlier days, new drugs were discovered by using traditional drug discovery techniques. Traditional techniques involve a search for active ingredients in and from natural sources; random screening of NCEs produced by chemical synthesis; trial and error method of using multiple new synthetic compounds or products isolated from natural sources; accidental discovery; and the ethnopharmacological approach based on integration and utilization of several disciplines such as chemistry, botany, pharmacology, and others. These techniques were used previously as essential skills for new drug discovery. These skills would not be adequate and would fall short of in the present-day competitive environment of new drug developmental research.

Presently the world over, different kinds of new approaches are taken for the discovery of new molecules that are rated as first-in-class. In one approach which is considered as classical, the phenotypic changes[3-5] either in the diseased whole life-forms of organisms (animal models) or of tissues or cell phenotypes, observations are made using the synthesized new small or large molecules or active ingredients isolated from plant or animal sources. Phenotypic screening is a strategy. Assay results form the basis of screening. The team of lead investigators is generally a group of highly talented medicinal chemists, biochemists, analysts specializing in the use of highly sophisticated instruments, biologists, pharmacologists, and clinicians with profound knowledge in medicinal chemistry. They also create access to expertise in rDNA technology for the synthesis of biological entities for use as drugs wherever rDNA-based biotech drugs are being invented. In their investigation, once a significant phenotypic change is observed in an evaluating model, the next step is to look for the target or targets where the new substance brings in phenotypic changes. Phenotypic methods of drug discovery are often considered as empirical as the search relies on phenotypic measurements of responses.

The other approaches of present-day novel API discovery methods include mainly two major techniques, which are ligand-based drug designing and structure-based drug designing. In both approaches, knowledge of biological targets of interest is necessary. Biological targets are chemically defined 3D structures in a living organism to which an endogenous substance including a chemical entity can bind to cause a change in the behavior or function of the living organism. When the biological targets bind to chemical entities causing a change which is drug-like manifestations, which include a desirable therapeutic effect

or an untoward adverse effect, then the biological targets are designated as the drug targets. The ligand-based drug design utilizes the knowledge of known molecules that bind to the defined drug targets of interest; based on this knowledge, a model of the drug target is built and this model, in turn, is used to design new molecules. Presently, for drug discovery purposes, multiple drug targets have been elucidated. Drug targets are pharmacologically active entities. These are associated with a particular disease process and can be probed by drugs to produce a desired therapeutic effect. Drugs would bind to the targets, sometimes in competition with one or more ligands from within the organism. The binding of a drug to the targets results in a change in the behavior or function of the living organism. The nature of binding can be non-covalent, reversible-covalent, or irreversible-covalent. There is no direct change in the biological target, but a conformational change in the target may be induced by the binding which would result in a change in the target function. Structure-based drug design works by finding out novel NCEs which would be complementing the 3D structure of a target molecule and would therefore bind or sit-on the complementing structure covalently or non-covalently or reversibly through hydrogen bonding or other physico-chemical bonding forces on the target site and thereby would affect a change in the biological target molecule.[6]

Small molecules covalently attached to certain target enzymes can inhibit their activity, thereby manifesting certain desirable therapeutic properties. There are many pharmacological advantages in such bindings by a reversible mechanism of action. Specific proteins such as *RAS* proteins, protein kinases, and some others have been studied, and new therapeutic substances have been discovered from such efforts. Care has to be taken in such routes of investigation to ascertain that the new therapeutic substances do not manifest intolerable toxicity and have negligible off-target binding properties. Novel small molecules that are discovered have the advantage of being more efficacious with prolonged therapeutic effects, thereby requiring lesser dosing, and are considered advantageous when treating chronic diseases such as cancer, asthma, or even certain infectious diseases. The prevalence and pharmacological advantages of covalent drugs, the potential risks, and challenges can be addressed through innovative design, and therefore novel small molecules acting through covalent binding present broad opportunities for new drug discovery.[7-9]

An updated databank exists in the public domain since 2018, known as DrugBank 5.0. This databank includes information on pharmacometabolomics which is part of science that analyzes and quantifies the metabolites existing in a biological material; levels of gene expression; as well as protein expression levels. This database can serve as an excellent starting point for multiple areas of novel drug discovery research. According to this database, there exist more than 4560 numbers of drug targets[10] in the whole area of proteins, DNA, RNA, and certain other macromolecules.

Coming back to the two major techniques for drug discovery, which are ligand-based drug designing and structure-based drug designing, the first one relies upon establishing relationships between the probing chemical structure of the new molecular entity and the pharmacological activity resulting from the binding of the chemical entity and the drug target. In this design, mathematically, the relationships between the chemical structure and pharmacological activity are determined and linked. Multiple regression and pattern recognition techniques are included and are known as quantitative structure–activity relationships (QSARs). QSAR methods can be described as the application of machine learning[11] and/or statistical methods to the problem of finding empirical relationships of any property of interest (say, a defined biological activity) of molecules and the calculated molecular descriptors of compounds being evaluated, using some empirically established mathematical transformation equations that should be applied to descriptors to calculate the property values for all molecules. Model validation is a critical component of model development in QSAR applications. Presently, the method has made substantial progress.

In the structure-based drug designing, also known as the pharmacophore model, a geometrical description of the chemical functionalities required of a ligand to interact with the receptor is worked out mathematically, based on the essential geometric arrangement of atoms or functional groups necessary to produce a given biological response. The features of a pharmacophore are the assembling of steric and electronic characteristics and attributes that are necessary to ensure optimum supramolecular interactions with a specific structure of a biological target. In this drug designing model, first, the 3D structure of the biological target is determined. The 3D structures are obtained either by X-ray crystallography or by NMR spectroscopy or by both. Thereafter, by using the 3D structure of the receptor, candidate drugs are predicted. The prediction is based on the values of binding capacities of the compounds with high affinity to the 3D structures. Computer-aided programs are used to determine the binding affinities.

In both ligand-based drug designing and structure-based drug designing, computational knowledge is essential and novel compounds can be designed and synthesized. The

novel compounds are then evaluated in the cellular or animal model and investigations would move further.[12]

Utilizing these models, discovery work can be carried out very fast. The key goal is to identify the most promising novel candidates from the experimental efforts to reduce the overall costs. High-end computer specialists having considerable knowledge in medicinal chemistry and biology are required to be inducted into the team.

Using the above techniques, novel APIs are designed and tested, wherefrom lead compounds evolve. With time when more targets are discovered, newer molecules would also evolve.

Future Indian research for the discovery of novel APIs would have to take recourse to the most modern methods of drug discovery. To attain success, best brains need to be inducted and extensive collaborative arrangements with industry need to be promoted while protecting the inventions with a stronger IPR regimen.

R&D expenditure by global pharmaceutical companies and success rate toward novel API discovery

The total global expenditure on R&D spent by the pharmaceuticals and biotechnologies during 2019 was estimated at US$ 168 billion, estimated to move up to US$ 182 billion by 2022 and growing at 2.8% CAGR (2015–2022).[13] The top major global pharmaceutical companies listed based on the ranking of sales of their recently launched novel formulations in 2015, based on using their recently discovered novel APIs, were Gilead Sciences, USA; Biogen, USA; GlaxoSmithKline, UK; Roche, Switzerland; Bristol-Myers Squibb, USA; Abb Vie, USA; Johnson & Johnson, USA; Astellas Pharma, Japan; Sanofi, France; and Pfizer, USA. The total sale of the novel formulations was placed at US$ 45.42 billion. Over seven years from 2015, by the end of 2022, as new APIs are expected to be emerging, several other companies are anticipated to perform better and the world ranking of sale of the 10 global companies for their novel API-based formulations would be Gilead Sciences, USA; Roche, Switzerland; GlaxoSmithKline, UK; Novartis, Switzerland; Bristol-Myers Squibb, USA; Sanofi, France; Johnson & Johnson, USA; Merck & Co, USA; Pfizer, USA; and AstraZeneca, UK. The anticipated turnover of these 10 companies from the sale of their novel products is about US$ 132.66 billion. The new situation and new positions are anticipated based on projections of the emergence of novel biotechnological drugs. To be a global leader, India needs to closely study the trends of research in these companies and the paths that are followed by them for achieving success. The R&D spending of these companies is indeed substantially high. For example, the R&D spending of the top 20 global companies, which include all the above-mentioned companies and some others, was US$ 89.6 billion in 2015 out of the estimated total global R&D spending of pharmaceutical companies of US$ 149.8 billion on R&D or about 59.8% of the total. But the spending of the large sum is not any guarantee for success. There is every need to analyze the key factors of success such as identifying and understanding the diseases, the disease process, inclusion of innovative processes within the task of accomplishment, build an efficient team with competent team leaders, increase skills of work as well as interpersonal skills, form collaborations with strategic partners, develop efficient managerial skills, and make provisions for firing if results are not forthcoming while having provisions for rewarding the more efficient ones out of the way to keep the system highly proficient.

It is to be kept in view in this context that the pharmaceutical industry globally is under growing pressure from a range of issues which include more stringhalt and greater demanding regulatory requirements for novel NCEs for approval as APIs; increasing costs of R&D; and inability to meet the prices for the expensive novel formulations coming out of novel APIs because of cost-constrained healthcare systems across the countries and considerable losses of revenue owing to patent expirations on their inventions. It has been mentioned that discovery of an approved novel API and its formulation takes on an average about 14 years, of which discovery of the NCE takes about 4.5 years, followed by preclinical testing of about 1 year, further followed by the conduct of the three phases of clinical trials which takes about 6.5 years, and finally another 1.5 years for submission of data to the regulatory authorities, obtaining approvals, and marketing. It has also been estimated that the overall probability of success for coming out with a novel API and its formulations in the market from the start of a project to regulatory approval and marketing is about 4.1% only, with breakups of 51% up to the discovery of an active NCE; about 69% from active NCE to up to reaching preclinical stage; about 12.8% from multiple phase trials; and about 91% during the submission phase.[14] It is reported[15] in another study that the overall success is about 4.9%. This study had analyzed 100 numbers of US FDA-authorized novel APIs, approved during the period 2006–2014 for 13 numbers foreign MNCs (with the numbers of new APIs approved), namely, Abbott/Abbvie, USA (1); Eli Lilly, USA (4); Roche, Switzerland (9); Sanofi, France (6); Merck & Co, USA (9); Pfizer, USA (11); AstraZeneca, UK (7); Novartis, Switzerland (13); Amgen, USA (6); GSK, UK (12); Takeda, Japan (6); Bristol-Myers Squibb, USA (9); and Boehringer Ingelheim, Germany (7). It was revealed that the

R&D expenditure per novel API worked out to US$ 3.27 billion, as high as US$ 31.29 billion. Closer scrutiny of the R&D costs of 61 novel APIs revealed that the range was from US$ 5.03 billion to US$8.70 billion. These numbers are huge for any company to spend and even for every developing country where the in-country developments are centrally planned. Many pharmaceutical companies are making innovative changes in their R&D policy approach and design to improve upon their overall efficiency. It is also to be taken note that the companies mentioned above are the topmost global companies where the salary structure and the amenities available to the employees are higher than most other companies, factors of which contribute to increased costs.

In another study[16] carried out on R&D costs of 106 novel APIs from 10 biopharmaceutical firms, it was estimated that the post-approval R&D costs on 2013 dollar prices were US$ 2.870 billion. The 2020 costs are projected by the author to be US$ 3.169 billion, taking into consideration the annual inflation rate during the period 2013–2020.

In yet another recent study[17] carried out based on the data on new therapeutic agents approved by the USFDA between 2009 and 2018 to estimate the research and development expenditure required to bring a new medicine to market, the mean expenditure was estimated at US$ 1336 million. During the study period, the USFDA had approved 355 new drugs and biologics and that the R&D expenditures were available for 63 products (about 18% of the total approved new drugs), which were developed by 47 different companies.

These costs provide a flavor of the quantum of investments required for turning out a novel API.

It may be mentioned in this context that Indian expenditure on R&D was never comparable to the level of R&D expenditure indicated earlier.

R&D investment in the Indian pharmaceutical industry

The R&D investment[18] of all Indian firms except Dr Reddy's and Ranbaxy hovered around 4% of sales during 2005–2006 to 2009–2010 and that only Dr Reddy's and Ranbaxy had spent more than 10% of their sales on R&D. Over the years, the R&D expenditure has not improved much. It was estimated that the R&D expenditure of the leading 10 pharmaceutical companies[19] in India including those of Zydus Cadila, Cipla, Lupin, Sun Pharma, and Torrent was about 8.5% of their total individual sales in 2018, which dropped to 8.4% in 2020. Indian expenditure in R&D has remained low. It is surmised by the author that the major Indian drug manufacturers had further reduced their R&D expenditure during the recent years to save expenditure and to remain cost-competitive in the environment of intense cost-cutting competition emanating from the competition faced by the Indian exporters in the US market pricing pressure, being the largest market for exports. In such an environment, novel API discovery remains in peril. The existing situation has to be changed, therefore.

An estimate of expenditure in India over a period hoping to succeed in discovering novel APIs and ways ahead

Indian policymakers and researchers would have to take the above success rates of MNCs into account, analyze each stage of drug development in its nitty-gritty, and find the gap areas for improvement to improve upon the overall success rate. India can also evolve its strategy and plan for the future. The huge costs contemplated should not be frightening because innovative methods and policies can be evolved to find the required amounts. Since the latest estimate for developing a novel API and its formulations has been estimated at US$ 1336 million, this figure has been considered to be the base for planning for India to develop novel APIs.

Taking into consideration the average time for discovery as 14 years, the annual requirement of R&D funds works out to US$ 95.43 million or about INR 668.42 crores per year per novel API. This figure can be used as the baseline figure to calculate the fund deployment. Assuming that India would plan to come out with 10 novel APIs over 14 years, the monetary deployment would be about INR 6684.2 crores per year. Finding such an amount of money would not be difficult if strong efforts are made. These calculations are based on the assumption that the novel APIs and their formulations would be in the market 14 years from start. Multiple benefits may likely start accruing much before the target period.

India has presently 1.46 crore taxpayers[20] and that in the Indian budget 2020, the gross tax revenue was pegged at INR 2,423,020 crores. As has been mentioned earlier, India has presently more than 3,000 pharmaceutical companies with a network of over 10,500 manufacturing facilities. The Indian domestic pharmaceutical market turnover[21] reached INR 1.4 lakh crores (US$ 20.03 billion) in 2019, increased by 9.8% from Rs. 129,015 crores (US$ 18.12 billion) in 2018. Pharmaceuticals export stood at US$ 20.70 billion in FY20. The turnover of the Indian pharmaceutical sector is expected to grow to US$ 100 billion by 2025.

The Indian government can raise the calculated monetary amount of INR 6684.2 crores per year from the above infrastructure to build an innovative novel API discovering infrastructure. India also has a pool of very ordinary farmers over 8.5 crores in numbers who have bank accounts

for receiving income support from the PM Kisan[22] program, which is a Central Government scheme. This huge pool of manpower can also be inspired by inducting them in the novel drug development and they would, it is believed, be ready to support the scheme by contributing a small sum of INR 10.00 per month, which would be INR 120.00 per year per individual farmer; the total sum that can come from this source can be INR 1020 crores, which is substantial. More than the money part, the involvement of common Indians in such a challenging endeavor has more nationalistic and patriotic feelings, which would inspire common men to come forward to assist.

The infrastructure and the policy formulation for this have to create adequate provisions of benefit sharing among the fund providers so that they are benefitted and the country as a whole reaps the benefits of becoming a dominant discoverer of novel APIs, many of which are expected to be jackpot discoveries.

The Indian government can create a not-for-profit Section 8, Schedule B, Public Sector Enterprise, under the administrative control of either the Ministry of Chemicals and Fertilizers, Department of Pharmaceuticals or the Ministry of Science and Technology, Department of Biotechnology, or can create a new set up like a Novel Drug Development Authority to be placed under the direct supervision of the Science and Technology Minister/Prime Minister. The enterprise shall work on a policy level as well as have an R&D laboratory to conduct research. The goals of the new entity shall be to improve the health of the nation by conducting relevant research that ultimately translates into the discovery of novel APIs that would be effective in treating difficult-to-treat diseases. The pathways need to include encouraging and conducting fundamental creative discoveries and their applications as the prime basis for protecting and improving human health. The research goals shall be to expand the knowledge base of the country in medical and associated sciences. The vision has to be to bring therapies to patients that significantly improve their lives. The efforts would also be to provide the discovered novel medicines at rational and affordable prices for patients who would use the medicines. Necessary supporting health insurance schemes should be evolved to support the prospective recipients to avail the benefits. For conducting mission-oriented research, either a new laboratory can be conceived and established or one existing national laboratory should be attached exclusively to the new enterprise. The efforts should be multidirectional but not infinite-directional. The efforts should be a judicious mix of specific Indian need-based gap-areas as well as global-need-based areas, so that the efforts when successful would benefit the common people as well as would hold potentials for meeting the sustainable business needs. To reduce unnecessary operational and avoidable infrastructure costs, optimization in the cost-saving moves should be a continuing feature of the new establishment. Other measures that may be useful to consider are (a) outsourcing of services linked with drug discovery that is available at cheaper prices and does not jeopardize the confidentiality of operation, (b) collaboration with centers of excellence which have special expertise in certain types of chemical synthesis, (c) clinical trial expertise/organization attached with renowned hospitals, etc., and (d) expert consultancy organizations that can assist in identifying expertise available elsewhere in clinical trials, regulatory affairs, safety solving issues, quality management issues, hiring of cGMP facilities for the manufacture of substances for a clinical trial, etc.

On September 25, 2014, the Indian government announced[23] the "Make in India" initiative to encourage manufacturing in India. The policy may have been announced to encourage foreign direct investment in multiple sectors, thereby inducting foreign technologies into India as fast as possible. The move was perhaps to have a quantum increase in multiple areas of the manufacturing sector's annual growth rate to increase the sector's share in the economy sizably, which was anticipated to contribute to additional jobs and to raise the contributions of the manufacturing in the Indian GDP to 25% by 2025 from the present 16%. The Drugs and Pharmaceuticals Industry is also within the ambit of the manufacturing sector. The pharmaceutical industry which is highly technology dependent is run globally by the foreign MNC leaders who are the possessors of technologies. Technologies are not shared easily, especially during the periods of their IPR-protected life-span. No MNC has come forward with any novel pharmaceutical technology to invest in India. In such a global environment, the responsibilities of developing novel technologies by national institutions and universities have increased enormously. Newer policy initiatives need to be propounded, therefore, to make the Indian public institutional infrastructure much more productive. There is a need to think out-of-the-box to bring more efficiency into the system. The Indian pride of supplying more cost-effective generic drugs globally is because India survives with small margins requiring paying lower salaries and wages to the skilled manpower and because of Indian's skills in chemistry and engineering sciences besides the availability of multiple numbers of capital goods and materials including auxiliary materials at more competitive prices. Also, there have been enormous efforts from time to time through both industrial and S&T policy supports to promote the Indian sector, especially the

Indian SMEs devoted to the production of pharmaceuticals including generic APIs. These efforts are considered highly appropriate for empowering Indian SMEs. However, these measures fell short of discovering novel APIs. Indian leadership shall brighten much further if it takes to crack the hurdles to invent novel APIs.

To become an important global player in the discovery of novel APIs during the coming years, India would need to spell out and spend on innovative multidisciplinary avenues with adequate provisions for enabling the inventors to adequately reap the benefits of their discovery in terms of societal recognition and amassing wealth. If this is not seriously taken note of and acted upon, talented young people will get diverted to other avenues of better remunerating areas such as the sales jobs in enterprises, banking and accounting jobs, powerful administrative jobs, and many others, in which the avenues for accruing wealth are presently easier for talented individuals. In such an environment, the country shall slide down over the years in comparison with other countries that are promoting inventions. The invention in new APIs holds the potentials of generating cutting-edge wealth for countries as these would prolong lives for the individuals suffering from difficult-to-treat/untreatable deadly diseases, a feat that cannot be matched with cost-effective generic APIs and their formulations, which appear much later in the Indian market only after the IPR protection has expired.

CONCLUDING REMARKS

India has made some mark in the discovery of novel APIs. In the meantime, India has emerged as a dominant player in the supply of bulk generic APIs all over the world. In years to come, India needs to emerge as an important new player for the discovery of novel APIs to sustain its present position. The new moves have to be novel and extraordinary. The medical doctors come across diseases and disabilities in people and look for means to keep people healthy; the biologists, biochemists, physiologists, and pharmacologists explore to know the mechanism and the effects of diseases; the medicinal chemists try to invent novel substances that are required to affect treatment; and the technologists venture to develop cost-effective manufacturing processes to provide these for use by the diseased individuals. The regulators decide on authorization for use of novel products. The policymakers decide on setting priorities taking into consideration the social, economic, and business needs and promote research so that inventions are made and novel medicines evolve, fostering the advancement of the country. The entrepreneurs work within this framework and invest and produce the finished substances that are consumed, and wealth is created in return and accrued. In this complex framework, novel policies are to be formulated which would act as the backbone of progress. The policy framework would evolve from the rightful inputs of all the actors, so that the integrated output produces successful results. Novel policies can evolve only by judiciously drawing from the strengths of each actor. Once the policy is framed, priorities are to be set with an action plan; it is implemented with periodic reviews and progress is made. Results would start getting visible after some time if the leadership is strong, the infrastructure is in place, and the actors are kept satisfied on showing results.

The moves would have to include selecting and building competent human resources with competent leaders. The infrastructure for the conduct of best-in-class research should be in place. Participation of all the actors including the government, the R&D institutions, the manufacturing pharmaceutical industry, and the common people of India are components, each of which may find a place in the endeavor. There should be provisions for weeding out incompetence.

The environment has to be most competitive with ready rewards for the achievers and provisions for firing incompetence. For a while, patience is required to extend enough time for the executors of research in multiple facets of inputs that determine success. A myopic rewards system based on influential and powerful individual assessments is dangerous for grand teamwork to succeed.

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REFERENCES

1. Differding E. The drug discovery and development industry in India—Two decades of proprietary small-molecule R&D. Chem Med Chem 2017;12:786-818.
2. Centaur Pharmaceuticals launches for the first time in the world – a New Chemical Entity (NCE) – 'WOXHeal®' in the treatment of Diabetic Foot Ulcer-Published by Free Press Journal (FPJ) Web Desk, Thursday, October 01, 2020. Available at: https://www.

freepressjournal.in/health/centaur-pharmaceuticals-launches-for-the-first-time-in-the-world-a-new-chemical-entity-nce-woxheal-in-the-treatment-of-diabetic-foot-ulcer [Last accessed on 2021 February 02].
3. Kotz J. Phenotypic screening, take two. SciBX 5. doi:10.1038/scibx.2012.380. Available at: https://www.nature.com/scibx/journal/v5/n15/full/scibx.2012.380.html. [Last accessed on 2021 April 08].
4. Swinney DC. Phenotypic vs. target-based drug discovery for first-in-class medicines. Clin Pharmacol Ther 2013;93:299-301.
5. Banik BK. A personal perspective on medicinal and pharmaceutical chemistry. Front Chem 2014;2:1-3.
6. Singh S, Malik BK, Sharma DK. Molecular drug targets and structure based drug design: A holistic approach. Bioinformation 2006;1:314-20.
7. Ghosh AK, Samanta I, Mondal A, Liu WR. Covalent inhibition in drug discovery. Chem Med Chem 2019;14:889-906.
8. Bauer RA. Covalent inhibitors in drug discovery: From accidental discoveries to avoided liabilities and designed therapies. Drug Discov Today 2015;20:1061-73.
9. Singh J, Petter RC, Baillie TA, Whitty A. The resurgence of covalent drugs. Nat Rev Drug Discov 2011;10:307-17.
10. Wishart DS, Feunang YD, Guo AC, Lo EJ, Marcu A, Grant JR, *et al*. DrugBank 5.0: A major update to the DrugBank database for 2018. Nucleic Acids Res 2018;46:D1074-82.
11. Popova M, Isayev O, Tropsha A. Deep reinforcement learning for de novo drug design. Sci Adv 2018;4:eaap7885.
12. Lionta E, Spyrou G, Vassilatis DK, Cournia Z. Structure-based virtual screening for drug discovery: Principles, applications and recent advances. Curr Top Med Chem 2014;14:1923-38.
13. World Preview 2016, Outlook to 2022 – Evaluate Pharma. Available at: https://www.google.com/url?sa=t&rct=j&q=&esrc=s&source=web&cd=&ved=2ahUKEwj_pseb4rPtAhXjjeYKHXtWAtsQFjABegQIBBAC&url=https%3A%2F%2Finfo.evaluategroup.com%2Frs%2F607-YGS-364%2Fimages%2Fwp16.pdf&usg=AOvVaw20fKeAhQv_2byPBGK-2n3j. [Last accessed on 2021 February 02].
14. Paul SM, Mytelka DS, Dunwiddie CT, Persinger CC, Munos BH, Lindborg SR, *et al*. How to improve R&D productivity: The pharmaceutical industry's grand challenge. Nat Rev Drug Discov 2010;9:203-14.
15. Schuhmacher A, Gassmann O, Hinder M. Changing R&D models in research-based pharmaceutical companies. J Transl Med 2016;14:105.
16. Di Masia JA, Grabowski HG, Hansenc RW. Innovation in the pharmaceutical industry: New estimates of R&D costs. J Health Econom 2016;47:20-33.
17. Wouters OJ, McKee M, Luyten J. Estimated research and development investment needed to bring a new medicine to market, 2009-2018. JAMA 2020;323:844-53.
18. Joseph RK. The R&D Scenario in Indian Pharmaceutical Industry. Discussion Paper No. 176. December 2011. Available at: https://www.ris.org.in/rd-scenario-indian-pharmaceutical-industry. [Last accessed on 2021 February 02].
19. India – R&D Spending by Top Indian Pharmaceutical .... Statista. Available at: https://www.statista.com/statistics/999279/randd-investments-share-by-pharma-companies-india/. [Last accessed on 2021 February 02].
20. How Many People in India Actually Pay Tax? Income Tax .... Available at: https://www.financialexpress.com/economy/how-many-people-in-india-actually-pay-tax-income-tax-department-clarifies-pm-modis-claim/1867332/. [Last accessed on 2021 February 02].
21. Pharma Industry in India: Pharma Sector Overview, Market ... Available at: https://www.ibef.org/industry/pharmaceutical-india.aspx. [Last accessed on 2021 February 02].
22. Kisan PM. Available at: https://pmkisan.gov.in/. [Last accessed on 2021 February 02].
23. Wikipedia contributors. (November 22, 2020). Make in India. In: Wikipedia, The Free Encyclopedia. Retrieved November 26, 2020. Available at: https://en.wikipedia.org/w/index.php?title=Make_in_India&oldid=990050388. [Last accessed on 2021 February 02].