Review Article

Novel Active Pharmaceutical Ingredients from India: The Actors-Part-I

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Abstracts Sixteen novel active pharmaceutical ingredients, namely Urea stibamine, Methaqualone, Enfenamic acid, Hamycin, Centimizole, Centbutindole, Ormiloxifene, Centpropazine, Centbucridine, Alpha-beta-arteether, Bulaquine, Chandonium Iodide, Sintamil, Amoscanate, Saroglitizar, and Diperoxochloric Acid (DPOCL), were discovered from India. Six formulations, namely of Ormiloxifene, Alpha-beta-arteether, Bulaquine, Sintamil, Saroglitizar, and DPOCL, are in the market. The Indian pharmaceutical industry uses nearly 2200 active pharmaceutical ingredients (APIs) for the manufacture of nearly 60,000 branded generic and generic formulations from its nearly 3000 manufacturing units. The industry manufactures nearly 1000 APIs locally and imports about another 1200 APIs; the manufacture of generic APIs as well as formulations is heavily dependent on imports. To remain a dominant manufacturer, India needs to invest in the discovery of novel APIs.

Keywords: Diperoxochloric acid, generic APIs, Indian pharmaceutical industry, novel APIs

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INTRODUCTION

India has presently more than 3,000 pharmaceutical companies[1] with a network of more than 10,500 manufacturing facilities. Indian pharmaceutical generic brands of formulations are the largest, with about 60,000 brands of medicines being manufactured and sold locally as well as exported, covering about 60 therapeutic categories. According to the estimate of the author, the number of generic APIs that are manufactured in India is about 1000, of which about 600 are significant ones with high export potential whereas the finished pharmaceutical formulations sold in India have in these a total of about 2200 APIs. About 1,200 bulk generic APIs are imported and used for the manufacture of finished formulations. Formulations of about 30 IPR-protected APIs are also sold in India. It is estimated by the author that from the beginning of the 17th century when Pharmacopoeia began to be used for allopathic systems of medicine, the number of active pharmaceutical ingredients used by humans for the manufacture of human medicines would not be more than five thousand and that presently, the world over about 3,000 APIs are being used for the treatment, mitigation, and cure of all kinds of human ailments and human diseases.

There are more than 2,700 generic API manufacturers in India, of which the majority are in the small-scale sector. The APIs

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manufactured in India in terms of value was about 8% of the value of the global API market in 2016–17; these APIs are accepted globally because of their internationally acceptable higher quality standards.[2] These facts indicate that India has generated competence in complex chemical synthesis; this is also because of its hold in innovative processes and deployment of low-cost skilled manpower, which are the main reasons, among others, for the attainment of such excellence. It is surmised that the in-country expertise can be harnessed gainfully if India can also emerge with multiple numbers of novel APIs. However, the number of new chemical entities (NCEs) approved and used as novel APIs from India was only 16 according to the author. These were Urea stibamine, Methaqualone, Enfenamic acid, Hamycin, Centimizole, Centbutindole, Ormiloxifene, Centpropazine, Centbucridine, Alpha-beta-arteether, Bulaquine, ChandoniumIodide, Sintamil, Amoscanate, Saroglitizar, and DPOCL. Certain other novel discoveries of APIs that were not synthetic but that were isolated from plant sources were Peruvoside,[3,4] a cardiac glycoside that was isolated from mature fruits of ThevetianerifoliaJuss; Gugulipids extracted and isolated from Guggul, an oleoresin obtained by tapping and injuring the Commiphoramukul tree; Bacosides, which are dammarane-type triterpenoid saponins isolated from Bacopa monnieri, a medicinal Ayurvedic herb that has been in use in the Indian system of medicine from ancient times to sharpen intellect and attenuate mental deficits; Consap, a sterile contraceptive cream produced from the saponins obtained from soap nuts of the plant Sapindusmukorosii (commonly known as Reetha in North India); and DalZbone, a product developed from the leaf extracts of Sheeshamtree (Dalbergiasissoo).[5] Among the novel 16 synthetic APIs discovered in India, formulations based on the six APIs, namely Ormiloxifine or Centchroman (Trade Names of formulations: Chhaya, Saheli, Novex-DS, Centron, and Sevista,[6] Alpha-beta-arteether (Trade name of formulation: E-Mal),[7] Bulaquine (Trade name of formulation sold with chloroquin: Aablaquin),[8] Nitroxazepine (Trade name: Sintamil), and Saroglitizar (Trade name of formulation: Lipaglyn),[9] and DPOCL (Trade name: WOXheal) are presently (January 2021) available in the market. Three of these products are from CSIR-CDRI, a National Laboratory, one from a foreign multinational company (MNC), and two from Indian companies. The other products invented in India, such as Enfenamic acid, Centinizole, Centbutindole, Centpropazine, Centbucridine, and Chandonium Iodide, were marketed by certain Indian companies who had procured the technology from CSIR-CDRI, a National Institute,[5] and Punjab University. It appears that the Indian companies could not capture an adequate market for these products in India. There are no indications in the literature as to whether intensive efforts were made for overseas marketing of these products. The therapeutic indications for which these novel APIs are approved are still relevant in medicine. Hamycin,[10] a polyene antifungal antibiotic developed by Hindustan Antibiotics Ltd (HAL), Pune also disappeared from the market probably because HAL became sick and had to discontinue its fermentation production activities.

For a country of Indian magnitude, the number of novel APIs discovered is, indeed, quite small. In this article, efforts have been made to assess the newer innovative steps that need to be taken to enable India to emerge as a dominant global player in the discovery and manufacture of novel APIs.

THE INTENT OF THE ARTICLE

This article intends to focus on the Indian discovery of new chemical entities that have been discovered and used as new APIs together with their formulations as new pharmaceutical formulations. The intent of the research work carried out for the development of new APIs that are chemically well characterized has been described. This area requires massive R & D investment. Indian research in this area is quite selective, and only a few companies have invested in this area of pharmaceutical research. The novel drugs manufactured by deploying r-DNA technology have not been included in this review. A search had been made for the new chemical entities that found use as new APIs developed in India for the first time in the world and that were later formulated and approved as usable pharmaceutical formulations for human use.

In the Indian context of new drug discovery, it requires to be mentioned that within the scope of the limited resources, several noteworthy developments took place, and these emanated especially due to the zeal and devotion of a small number of outstanding researchers and scientists. Special mention needs to be made of the developments that took place from the 1950s and thereafter when certain government-run organizations got themselves prepared for this mission. Certain private institutions run by the private industry, including certain foreign multinational companies, were also fully committed to this venture of the discovery of new drugs, as has been briefly described.

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 forty API manufacturing units were also consulted to

obtain information. In addition, 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 also 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. Besides, the author also worked in several Indian government departments dealing with the policies and practices on the Indian drugs and pharmaceutical industry.

INDIAN ACHIEVEMENTS IN DEVELOPMENT OF NOVEL APIs

The discovery of 16 novel APIs by Indian scientists 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 in discovery and invention. Inventors are a separate class of people who are to be incessantly encouraged to remain focused on their tasks by providing all the necessary amenities and support. Their efforts bear fruits when they receive all-around support. 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.

The allopathic system of medicines was introduced in India during British rule. In late 1800 AD, the British government was highly concerned by the deaths and disabilities of people, especially of the British rulers, from a wide range of tropical diseases. These diseases included plague, rabies, cholera, diphtheria, tetanus, pertussis, typhoid fever, diarrhea and dysentery, leishmaniasis, leprosy, trypanosomiasis, lymphatic filariasis, cysticercosis, helminthiasis, and several others. Many of these diseases were researched upon by the British rulers; they set up several vaccine institutes in India to conduct research and to produce vaccines to treat several of these tropical diseases in late 1800 AD. The development of vaccines was considered the best option at that time than any other option for winning over the diseases. As a consequence, 15 vaccine institutes[11] were established by the British rulers. The establishment of these institutes at the beginning of the 1890s ushered modern medical research into the country.

During the prevailing scenario existing in the early years of 1900 AD, it was difficult to carry out research in chemotherapeutic substances. The German scientist Paul Ehrlich's idea[12] of "magic bullets" proposed in 1900 AD could not be pursued by the then government because of various constraints and these were, indeed, not pursued by the British rulers at that time in India. Synthetic organic chemistry was not very strong during these periods. Paul Ehrlich proposed in 1900[13] that just like when a gunshot is made, propelling a bullet to hit a specific target, so also there could be chemicals that could be used to specifically target the invading microorganisms. In 1909, this concept of "magic bullet" was also established and elaborated by Ehrlich himself through his discovery of Salvarsan. Salvarsan was used for the treatment of syphilis and trypanosomiasis (sleeping sickness). The drug was introduced at the beginning of 1910. This was an organoarsenic compound. Another name of Salvarsan is Arsphenamine.[14] Because of the constituents of this compound, it containing arsenic, it was found to be substantially toxic to humans and was later discontinued. However, during the prevailing time, this was an outstanding contribution to humankind.

The researchers in the early years of 1900 AD could not easily pursue investigations in chemotherapeutic substances in India. From the study of the various contemporary literature, the author felt that this was essentially because of the scarcity of starting chemicals, inadequate research infrastructure, and less advancement in the country in the pursuit of chemical synthesis. Raw materials were essentially inorganic.

From that time onward, up to the present time, India made contributions toward the discovery and manufacture of novel APIs of various kinds. Table 1 provides the synopsis of Indian discovery.

Of the 16 novel APIs discussed earlier, the first 15 NCEs were developed purely from Indian efforts whereas the sixteenth one, namely DPOCL, was codeveloped through a collaboration between Centaur, Mumbai, and Cyto Tools AG, Germany. Centaur Pharmaceuticals Private[49] Ltd (Centaur), Mumbai entered into a collaboration about 15 years ago, with CytoTools AG, Germany to codevelop a promising new molecule by the namely DPOCL, which belonged to CytoTools. The molecule was to be tested for the treatment of diabetic foot ulcers. The molecular formula[50] of DPOCL is $\mathbf{Cl_2O_6}$ and its molecular weight is 166.9 g/mol. DPOCL is stated to have been protected by patents in multiple countries by Cyto Tools. Centaur had conducted Phase II trials on DPOCL in India in 2010 and later conducted Phase III trials[51] on the formulation derived from DPOCL. Based on the results of Phase III

Table 1: Novel APIs with names of institutes/organizations/companies, inventor/s, year, commercialization, etc

Serial no	Name of the novel API & [therapeutic indication]	Discovered at institute/ company	Name/s of the discoverer/s and [references]	Year of discovery	Technology transferred to industry and year of transfer	Whether in Indian market in January 2021	Remarks
1	Urea stibamine[15-17] [Anti-leishmaniasis drug]	Campbel	Brahmachari U N	1923	Formulation used extensively on patients	No	The inventor and others extensively used the medicine on patients.
2	Methaqualone[18-19] [Sedative/ hypnotic]	CSIR-IICT	Kacher I K and Zaheer S H	1951	–	No	Presently banned in India, being a narcotic drug. Extensively used earlier in other countries
3	Enfenamic acid [20-22] [Analgesic]	CSIR-IICT	Sattur P B and Hashim R	1964	Transferred to Unichem Lab, Mumbai	No	Commercialized in 1981, but abandoned later
4	Hamycin[10,23] [Antifungal antibiotic]	HAL	Thirumalachar M J	1966	HAL manufactured and sold	No	HAL became sick and could not continue manufacture.
5	Centimizone[24-25] [For treating thyroid disorder]	CSIR-CDRI	Anand N and Karkun, J. N	1962	Transferred to Unichem Lab, Mumbai	No	Never marketed
6	Centbutindole (INN-Bripurone),[26] [Antipsychotic agent, a dopamine antagonist]	CSIR-CDRI	Saxena AK, Jain PC, Anand N and Dua P R	1973	Transferred to Chemosyn, Mumbai in 1987	No	Never marketed
7	Ormiloxifene (also known as Centchroman)[27-32] [A non-steroidal selective estrogen receptor modulator]	CSIR-CDRI	Ray S, Kamboj V, Grover P, A. Kar A and Anand N	1975	Technology transferred to multiple Indian companies	Yes	Formulation available in the market as 'Saheli','Centron','Chhaya'.
8	Centpropazine[5, 33, 34] [Antidepressant drug]	CSIR-CDRI	Rastogi S N, Anand N, Prasad C R, Gupta P P, and Sharma J N	1972	Technology transferred to Merind Ltd., Mumbai in 1996	No	Never marketed
9	Centbucridine[5,35,36] [Local anesthetic]	CSIR-CDRI	Patnaik G K, Rastogi S N, Anand N and Dhawan BN	1982	Technology transferred to Themis Chemicals Mumbai in 1987	No	Never marketed
10	α/β-Arteether[5,37] [Anti-malarial drug]	CSIR-CDRI	Bhakuni R S, Singh T, Kahol A P, Tewari A, Tandon S and Khanuja S P S	2003	Technology transferred to Themis Medicare Mumbai in 1997	Yes	Available in market as 'E-Mal an injectable formulation
11	Bulaquine[5,38,39] (Elubaquine) [Anti-malarial drug]	CSIR-CDRI	Bhat B K, Seth M, Bhaduri A P	1984	Technology transferred to Nicolas Piramol, Mumbai in 1999	Yes	Available in market as Aablaquin
12	Chandonium iodide[5,40,41] (now known as Candocuronium iodide) [Skeletal muscle relaxant]	Punjab Univ. and CSIR-CDRI	Gandiha A, Marshall I G, Paul D and Singh H	1974	Technology transferred to Ranbaxy, New Delhi in 1987 and to Cipla, Mumbai in 1995	No	Commercialized but abandoned later
13	Nitroxazepine[42-43] (Sintamil) [Antidepressant]	Hindustan Ciba-Geigy (taken over by Novartis)	Described by Nagarajan K and Arya V P	Before 1972	Product introduced in the market in 1982 by the Hindustan Ciba-Geigy	Yes	Being sold as Sintamil formulation

Table 1: Continued

Serial no	Name of the novel API & [therapeutic indication]	Discovered at institute/ company	Name/s of the discoverer/s and [references]	Year of discovery	Technology transferred to industry and year of transfer	Whether in Indian market in January 2021	Remarks
14	Nithicocyamine[42,44] (Amoscanate)	Hindustan Ciba-Geigy (taken over by Novartis)	Described by Nagarajan K and Arya V P	1976	Formulation approved by Indian Regulatory authorities in 1985	No	Markedly toxic for human use
15	Saroglitizar[45-47] [Antidiabetic drug]	Zydus Cadila (Cadila Health care)	Lohray B B, Lohray V B, BarotV K G, Raval S K, Raval P S and Basu S	2001	Formulation marketed by the company in 2013	Yes	Marketed by Zydus with trade name 'Lipaglyn'
16	Diperoxochloric acid [To treat diabetic foot ulcers]	Cyto Tools AG,[48] Germany	Dr Mark-Andre Freyberg and Dr Dirk Kaiser	Centaur teamed up for co-development of it with Cyto Tools about 15 years back	Formulation was marketed in India by Centaur in 2020	Yes	Marketed by Centaur under the trade name 'WOXheal'

trials, the drug was approved for human use in India by the DCGI in 2020. The novel formulation of DPOCL was launched by Centaur[52] in October 2020 by the trade name 'WOXheal' and this was indicated for the treatment of diabetic foot ulcer.

Indian companies have concentrated, in general, on the development of modern pharmaceutical formulations in the allopathic system, using already available APIs. As India is also known to be using a wide range of traditional medicines described in multiple numbers of traditional treatment systems such as Ayurveda, Siddha, and Unani, several companies have resorted to manufacturing and selling formulations based on these systems of medicines, mostly by using herbal starting materials and ingredients. In the allopathic system of medicines, where the pharmaceutical formulations are manufactured using APIs approved by the regulatory authorities under the law, several companies have set up their API manufacturing facilities from where the APIs produced are either used for in-house consumption or sold to other buyers, including the importers. The APIs manufactured generally fall within the category of generic drugs. Several companies in India have also developed innovative new combinations of generic APIs as well as pharmaceutical formulations of better types by regulating the delivery mechanism of the active ingredients. The use of such formulations requires the generation of information in an animal model for safety and efficacy followed by generating clinical data on human subjects. As a result, establishments and facilities for preclinical and clinical research have also emerged in the country.

Novel synthetic methods of known APIs are essentially an effort that took roots in India in the late 1960s and especially during the decade of 1970s after the Indian Patents Act 1970 was promulgated; this Act abolished product patents for pharmaceutical active ingredients. Earlier, due to various reasons, especially due to the poor availability of minimum interdisciplinary infrastructure in the country in general as also due to the nonavailability of adequate trained manpower, the research for the synthesis of known drugs was moving at a snail's speed. The then Indian Patents system was a great hindrance to carry out further research on the IPR-protected molecules, as any novel process not described in the specifications of the IPR-protected molecules was also deemed to be protected as per the law. The availability of petrochemical-based raw materials was scarce due to the nonavailability of the petrochemical-based industry. The organic raw materials were based on coal-tar fraction-based products that were scanty in availability and were expensive too. The fermentation-based ethyl alcohol, which served as the starting material for many active substances, synthesized or extracted was also in short supply and was not freely available.

A couple of technologies for the manufacture of certain antibiotics from the basic stage were procured by the Indian government through its two public sector understandings in the early 1950s (Hindustan Antibiotics Ltd, Pune) and mid-1960s (Indian Drugs and Pharmaceuticals, at Rishikesh and Hyderabad). Only after the new Indian Patents Act 1970 was promulgated in 1972, great progress was visible

in medicinal chemistry research in India. Efforts were made primarily through chemical synthesis to invent non-infringing novel processes for the manufacture of already known APIs that were active against a wide range of diseases and disabilities. Some efforts were also directed toward the discovery of novel APIs. Certain diseases, especially those endemic to the tropical climates, were especially concentrated upon. The therapeutic areas chosen were the development of novel anthelmintics (against hookworm, roundworm, tapeworms, and flukes), antiprotozoal drugs (against malaria and trichomoniasis), anti-dysentery and anti-diarrheal drugs (against amoebiasis and giardiasis), antiviral drugs, analgesics, antidiabetic drugs, cardiovascular drugs, anti-lipidimics, molecules acting on the central nervous system including anti-hypnotics, local anesthetics, and many others.

In the meantime, the Indian generic API industry registered phenomenal growth and became an organized, globally competitive industry. The strong and determined policy push of the government coupled with the intense efforts of the entrepreneurs in India comprising both the public sector and the private sector actors, including the foreign MNCs, were instrumental to the development of local API and the pharmaceutical formulations manufacturing industry. India is presently the largest supplier of generic drugs globally. The APIs are the largest segment of the Indian pharmaceutical market; APIs are synthetic chemical entities (including the high potency active pharmaceutical ingredients) as well as biotech APIs. This article is all about APIs originating from chemical synthesis. Biotech-based drugs produced by deploying r-DNA technology and others that evolved from other biotechnology methods are not discussed here.

INDIAN INITIATIVES TOWARD INVENTING NOVEL APIs

Government-owned institutions and companies

Among the government-owned Indian institutions and public sector units, on the R & D work done for the discovery of new drugs after India's independence, mention must be made of the Regional Research Laboratory, Hyderabad (later renamed as CSIR-Indian Institute of Chemical Technology (CSIR-IICT), Hyderabad); the All India Institute of Medical Science (AIIMS), New Delhi; Hindustan Antibiotics Ltd, Pimpri, Pune, Maharashtra; CSIR-Central Drugs Research Institute (CSIR-CDRI), Lucknow; Punjab University (PU), Punjab; the Regional Research Laboratory, Jammu (renamed as CSIR-Indian Institute of Integrative Medicine); CSIR-Indian Institute of Chemical Biology, Kolkata; CSIR-Institute of Microbial Technology, Chandigarh; CSIR-Institute of Genomics and Integrative Biology, Delhi; CSIR-Central Institute of Medicinal and Aromatic Plants, Lucknow; CSIR-Centre for Cellular and Molecular Biology, Hyderabad; CSIR-National Chemical Laboratory, Pune; CSIR-Institute of Himalayan Bioresources Technology, Palampur; CSIR-Industrial Toxicological Research Centre, Lucknow; CSIR-National Botanical Research Institute, Lucknow; and CSIR-Central Salt and Marine Chemicals Research Institute, Bhavnagar, Gujarat, India. In all these institutes also, besides multiple types of investigation work is being carried out to discover novel active pharmaceutical ingredients within their mandated research work. Although all these institutes have immensely contributed to newer and novel understanding in various facets of the cellular and molecular biology of different life forms, only CSIR-IICT, CSIR-CDRI and PU have come out with a few defined novel APIs, as mentioned in Table 1.

Foreign multinational companies

Among the foreign multinational companies, the R & D work by Hindustan Ciba-Geigy at Ciba-Geigy Research Centre, Bombay (later renamed as Hindustan Ciba-Geigy) is most significant. Two novel synthetic drugs emerged from their research, as observed in Table 1. The company decided to discontinue further basic research using the skills of synthesis at their Goregaon research facilities because of inadequate return from the efforts. They continued their research work for 25 long years in India. The decision of Hindustan Ciba-Geigy to close down the chemotherapeutic research center was a great loss to India. Research carried out by several other foreign multinational companies and their affiliates, such as Hoechst Research Centre, Bombay; Smith Kline and French, Bangalore; Astra-IDL Ltd, Bangalore; Boots India Ltd, Bombay; and certain others, was also significant. However, no new drugs emerged from their research efforts that obtained regulatory approval for use in human subjects. Most of these multinational companies later on either merged with other multinational companies or were acquired by others. Astra Research Center, Bangalore was established in 1985 and was later named the AstraZeneca R & D Center after the merger of Astra and Zeneca. In January 2014, the management decided to close down the Research Centre. It was again a great loss to the country.

The closing down of the R & D units of the foreign MNCs in India was a strong signal for the country to rethink and ponder what was preventing the multinational companies to carry out basic and application-oriented research for drug discovery in India, even though India had a sizable

number of trained manpower and that the developmental infrastructure in the country was comparatively cheaper.

Another significant point worth noting is that in the new Indian licensing policy, though presently 100% foreign direct investment is possible in the pharmaceutical industry there is myopic interest in foreign MNCs to invest in India in projects requiring the establishment of infrastructure for the deployment of API production technologies. Consequently, foreign MNC efforts in deploying basic technologies and linked activities through R & D endeavors in India do not seem to create appetite for the foreign MNCs in the existing environment of policies in the country.

In an earlier study[53]on the Indian government policies on the development and growth of the pharmaceutical industry, it was argued that since India's independence the government policies were aimed at reducing foreign dependence on medicines and at boosting the local production of APIs through policy support by regulating the industrial licensing endeavor and by modifying the Indian Patent policy to enable the development of a strong API production base through the persuasion of usage of local materials aiming at Indianisation and at supporting the local industry through pricing support (enabling them to recover cost plus revenues). Such policies pursued up to the time of India's decision to join WTO did well up to 1991. Thereafter, when India opened up to liberalization in July 1991 followed by India's joining the WTO in April 1994 and further followed by amending the Indian Patents Act from 01.01.1995 whereby product patenting rights were reinforced, the local pharmaceutical industry was put to severe international competition and the local API industry was severely affected. Only those companies that had access to highly productive technologies survived and even flourished. Foreign MNCs and other foreign establishments did not invest in India for the production of APIs nor were there also any endeavors from them for conducting R & D toward novel API development. Some foreign investment that took place was for acquisition of Indian pharmaceutical companies producing generic APIs and biotech pharmaceutical products, such as the purchase of Matrix Pharmaceuticals, Hyderabad by Mylan Laboratories, USA; Shantha Biotechnics, Hyderabad by Sanofi-Aventis, France; procurement of majority equity in J.B. Chemicals and Pharmaceuticals Ltd, Mumbai by the US private equity giant KKR, etc.

Indian private companies

Among the Indian private sector industries, significant efforts were made by several companies in various ways. The efforts made by the following companies, arranged in alphabetical order, were analyzed from the information available on the websites of these companies. These companies were chosen by the author based on his knowledge and experience of interactions of the author with many of these companies. The companies selected were: Aarti Drugs Ltd, Palghar, Maharashtra; Alembic Pharmaceuticals Ltd, Vadodra; Aurobindo Pharma, Hyderabad; Biocon Ltd, Bangalore; Cadila Laboratories, Ahmedabad; Centaur Pharmaceuticals Private Ltd, Mumbai; Century Pharmaceuticals, Mumbai; Cipla, Mumbai; Dabur Research Foundation and Dabur Pharma Limited, Gaziabad, UP; Dr. Reddy's Laboratories, Hyderabad; Divi's Laboratories, Hyderabad; Elder Pharma, Mumbai; Emcure, Mumbai; FDC Ltd, Mumbai; Glenmark Pharmaceuticals Limited, Mumbai; Granules India Limited, Madhapur, Hyderabad; Hetero Drugs, Hyderabad; IOL Chemicals and Pharmaceuticals Limited, Ludhiana; IPCA Labs, Mumbai; J B Chemicals and Pharmaceuticals Ltd, Mumbai; Jubilanr Pharma, Noida, UP; Lupin Ltd, Mumbai; Mankind Pharma, New Delhi; Marksans Pharma Ltd, Goa; Matrix Pharmaceuticals, Hyderabad; Natco Pharma, Hyderabad; Nicholas-Piramal, Mumbai; Orchid Pharma, Chennai; Panacea Biotech, Delhi; Ranbaxy laboratories, New Delhi and its Ranbaxy Research Foundation; Reliance Life Sciences, Mumbai; Sarabhai Chemicals, Vadodra (at its Sarabhai Research Centre, Baroda); Shilpa Medicare

Table 2: List of major innovation programs based on PPP in India for promoting drug development

Government Agency	PPP programs for major innovation in India and year of starting
Department of Science and Technology (DST), Ministry of Science and Technology	Technology Information, Forecasting and Assessment Council (TIFAC) (1988) Drug and Pharmaceuticals Research Programme(1994–95) Technology Development Board (TDB) (1996)
Council of Scientific and Industrial Research (CSIR), Department of Scientific and Industrial Research, Ministry of Science and Technology	New Millennium Indian Technology Leadership Initiative (NMITLI) (2000–01) Open Source Drug Discovery (CSIR-OSDD) (2008)
Department of Biotechnology (DBT), Ministry of Science and Technology	Small Business Innovation Research Program of India (SBIRI) (2005) Biotechnology Industry Partnership Program (BIPP) (2009) Biotechnology Industry Research Assistance Council (BIRAC) (2012) to serve as a single window for promoting innovation-led biotechnology research Biotechnology Ignition Grant (BIG) of BIRAC after 2012 Contract Research and Services (CRS) of BIRAC after 2012

Ltd, Hyderabad; Sun Pharmaceuticals, Mumbai; Suven Pharmaceuticals, Hyderabad; Syngene International Pvt Ltd, Bangalore; Torrent Pharma, Ahmedabad; USV Ltd., Mumbai; Unichem Labs Ltd., Mumbai; Wockhardt Ltd, Mumbai; ZCL Chemicals, Mumbai; and Zydus Cadila, Ahmedabad. Most of these companies are among the dominant ones in the API business.

Sarabhai group was at one time a dominant manufacturer of a large number of synthetic APIs and APIs manufactured by fermentation methods. Some of these companies mentioned here have made a substantial investment in search of novel APIs. A sizable number of inventions made by many of these companies have been protected by IPR. These companies and other Indian manufacturers of generic APIs have found a couple of NCEs. However, none of the discovered NCEs could come up to the stage of regulatory approval as a novel API except only one NCE, which was Saroglitizar, an antidiabetic drug discovered by Cadila Healthcare, a sister concern of Zydus Cadila Group, Ahmedabad. Another company, Centaur Pharmaceuticals Private Ltd, Mumbai came out with a new API, DPOCL, and its formulation through teaming up an arrangement with Cyto Tools AG, Germany. However, these companies and many others are producing a large number of generic APIs, estimated to be about 1,000 in number, of which about 600 have strong export potential and are, indeed, contributing positively toward foreign exchange earnings for India.

NEW INITIATIVES BY INDIAN GOVERNMENT FOR INVENTING NOVEL APIs

The government of India from various scientific departments of the Ministry of Science and Technology has attempted concerted efforts toward promoting the development of the drugs and pharmaceuticals industry, including the development of a wide range of APIs, especially in the public-private partnership (PPP) model. Table 2 summarizes the major efforts made by the government in this direction along with the years when each of these inventive policies and plans were initiated.

All the programs, schemes, and projects of DST, CSIR, and DBT just cited had made a noticeable impact on promoting research, technology development, and industrialization through SMEs in the country and in developing the drugs and pharmaceuticals industry. However, no novel API emerged from these multiple endeavors.

Before these efforts, the Government of India had instituted another novel program from the Ministry of Earth Sciences[54] to Indian marine resources for the discovery of novel drugs. The Ministry of Earth Sciences had instituted a program in 1990 under the leadership of the Central Drugs Research Institute (CDRI), Lucknow, and involved besides CDRI another 14 Indian institutions and universities, namely (a) National Institute of Oceanography (NIO), Goa; (b) Central Salt and Marine Chemicals Research Institute (CSMCRI), Bhavnagar; (c) Indian Institute of Chemical Technology (IICT), Hyderabad; (d) Institute for Minerals and Materials Technology (IIMT), Bhubaneswar; (e) National Institute of Ocean Technology (NIOT), Chennai; (f) Advanced Centre for Treatment, Education and Research (ACTREC), Mumbai; (g) Central Institute of Fisheries Education (CIFE), Mumbai; (h) Department of Fisheries, Government of West Bengal, Kolkata; (i) Toppiwala National Medical College, Mumbai; (j) Andhra University, Visakhapatnam; (k) Calcutta University, Kolkata; (l) Annamalai University, Parangipettai; (m) University of Madras, Chennai; and (n) Central Marine Living Resources and Ecology, Kochi. The Consortium was formed by bringing together the 15 institutions and universities across the country, and it was believed to be useful and productive as the cross-institutional collaboration and the leveraging of human resources from a different environment was thought to integrate ideas from multiple thought processes and efforts that resulted in a productive outcome. However, the multi-institutional efforts put forward during the long period of nearly three decades yielded very little in terms of the discovery of novel APIs.

Therefore, there is much justification to ponder as to why the results were not exciting in the context of novel drug discovery from these multiple efforts. No novel API has yet emerged from any of these government programs.

DISCUSSION AND CONCLUDING REMARKS

India has made phenomenal progress in becoming an important global player in the manufacture and supply of generic APIs and generic as well as branded generic formulations. It is believed by the author that the major 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 of novel APIs.

India has made some mark in the discovery of novel APIs. In the meantime, international competition in the open-market economy has brought in intense competition and so that India maintains its present position and excels further, much more has to be done. In years to come, India needs to emerge as an important player in the discovery of novel APIs too. There is an urgent need to study what

factors and issues are creating impediments toward India's emergence as an important global player in the discovery of novel APIs.

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Conflicts of interest

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REFERENCES

1. The pharmaceutical industry in India: Invest in Pharma Sector. https://www.investindia.gov.in/sector/pharmaceuticals
2. Vyas V. API, largest segment of Indian pharmaceutical market. News. Phaemabiz.com, Jan 30, 2020-: http://www.pharmabiz.com/NewsDetails.aspx?aid=121677&sid=21
3. Rangaswami S, Venkata RE. New crystalline glycosides from the seeds of ThevetianeriifoliaJuss. J Sci Industr Res (India) 1958;17B:331-2 and Rangaswamy S and Venkat RE, 1959 J. Sci. Ind. Res. BI8 445.
4. Bhatia ML, Manchanda SC, Roy SB. Haemodynamic studies with peruvoside in human congestive heart failure. Br Med J 1970;3:740-3.
5. CSIR-CDRI | Home. https://cdri.res.in/
6. Wikipedia contributors. (2021, January 6). Ormeloxifene. In Wikipedia, The Free Encyclopedia. Retrieved January 16, 2021. https://en.wikipedia.org/w/index.php?title=Ormeloxifene&oldid=998682539 [Last accessed on Jan 16, 2021].
7. Buy EMAL INJECTION 150MG - Apollo Pharmacy. https://www.apollopharmacy.in/emal-injection-150mg.html
8. Bulaquine combination Price of 2 Brands / Trade Names .... https://www.medindia.net/drug-price/bulaquine-combination.htm
9. Lipaglyn Tablet: View Uses, Side Effects, Price and https://www.1mg.com/drugs/lipaglyn-tablet-322621
10. Process of producing Hamycin antibiotic and product produced. US Patent No:3, 261,751 dated 19 July 1966 (has since expired). https://www.google.com/patents/US3261751
11. Lahariya C. A brief history of vaccines & vaccination in India. Indian J Med Res 2014;139:491-511.
12. Paul Ehrlich, In Wikipedia contributors. (2021, January 14). Paul Ehrlich. In Wikipedia, The Free Encyclopedia. Retrieved January 24, 2021. https://en.wikipedia.org/w/index.php?title=Paul_Ehrlich&oldid=1000261256 [Last accessed on Jan 24, 2021].
13. Wikipedia contributors. (2020, October 10). Magic bullet (medicine). In Wikipedia, The Free Encyclopedia. Retrieved January 24, 2021. https://en.wikipedia.org/w/index.php?title=Magic_bullet_(medicine)&oldid=982783039 [Last accessed on Jan 24, 2021].
14. Wikipedia contributors. (2021, January 11). Arsphenamine. In Wikipedia, The Free Encyclopedia. Retrieved January 24, 2021. https://en.wikipedia.org/w/index.php?title=Arsphenamine&oldid=999713512 [Last accessed on Jan 24, 2021].
15. Brahmachari UN. Chemotherapy of antimonial compounds in kala-azar infection. Part II. Dermal leishmanoid. Indian J Med Res 1923;10:948-52, https://www.cabdirect.org/cabdirect/abstract/19232901165
16. Brahmachari U. Chemistry of urea stibamine. Nature 1940;145:1021-2. https://doi.org/10.1038/1451021b0
17. Antimony treatment of kala-azar. Nature 1940;145:546. https://doi.org/10.1038/145546b0
18. Kacker IK, Zaheer SH. Synthesis of Substituted 4-Quinazolones. J Indian Chem Soc 1951;28:344-6.
19. Methaqualone ban. https://timesofindia.indiatimes.com/city/mumbai/Methaqualone-worth-Rs-27-5-crore-seized-in-Palghar-farmhouse-raid/articleshow/52351265.cms
20. Sudhindra BS. Self-consistent molecular modelling approach for receptor identification and rug design: Basis and database needs. J Indian Inst Sci 1987;67:1-27, http://journal.iisc.ernet.in/index.php/iisc/article/download/1137/1169
21. Tromaril, India Today. https://www.indiatoday.in/magazine/science-and-technology/story/19810228-indian-scientists-achieve-major-breakthrough-with-anti-inflammatory-drug-tromaril-772684-2013-11-26
22. Kshirsagar NA, Paul T, Sheth UK. Natriuretic activity of tromaril (RH-8): a non-steroidal anti-inflammatory agent, in normal volunteers. Br J Clin Pharmacol 1980;9:530-1.
23. Wikipedia contributors. (2019, September 14). Hamycin. In Wikipedia, The Free Encyclopedia. Retrieved November 4, 2020. https://en.wikipedia.org/w/index.php?title=Hamycin&oldid=915702586 [Last accessed on Nov 04, 2020].
24. Karkun JN, Anand N. Antithyroid activity of some 1-alkyl imidazolidine 2-thiones. Experientia 1962;18:181. https://link.springer.com/article/10.1007%2FBF02151717
25. From Ancient Medical Knowledge to the Modern Drug .... https://www.researchgate.net/publication/312040693_FROM_ANCIENT_MEDICAL_KNOWLEDGE_TO_THE_MODERN_DRUG_DEVELOPMENT_IN_INDIA
26. Saxena AK, Jain PC, Anand N. Agents acting on the central nervous system. 15. 2-substituted 1,2,3,4,6,7,12,12a-octahydropyrazino(2',1':6,1) pyrido(3,4-b)indoles. A new class of central nervous system depressants. J Med Chem 1973;16:560-4.
27. Ray S, Kamboj V, Grover P, Kar A, Anand N. A process for the synthesis of 2,2-disubstituted-3,4-diphenylchromans; 1975. Indian Patent Specification No. 129187, cited in Clinical pharmacokinetics and interaction of centchroman- A mini-review. http://www.contraceptionjournal.org/article/S0010-7824(09)00516-2/pdf
28. Singh MM. Centchroman, a selective estrogen receptor modulator, as a contraceptive and for the management of hormone-related clinical disorders. Med Res Rev 2001;21:302-47.
29. Saheli Tablets. https://lovematters.in/en/birth-control/types-of-birth-control/saheli-the-only-non-hormonal-birth-control-pill
30. Lal J, Nityanand S, Asthana OP, Nagaraja NV, Gupta RC. Optimization of contraceptive dosage regimen of centchroman. Contraception 2001;63:47-51.
31. About Centron, MedIndia. http://www.medindia.net/drug-price/ormeloxifene/centron.htm
32. Chhaya Tablet, MoH&FW. https://humdo.nhp.gov.in/new-contraceptives/
33. Rastogi SN, Anand N, Prasad CR. Agents acting on the central nervous system. 14. 1-(p-alkanoylphenoxy)-3-(N 4-arylpiperazinyl)propan-2-ols. A new class of antidepressants. J Med Chem 1972;15:286-91.
34. Rastogi N, Anand N, Gupta PP, Sharma JN. Agents acting on central nervous system 19 . . . as local anesthetics, hypnotics, and tranquilizers. J Medicinal Chem 1973;16:797-804.
35. Patnaik GK, Rastogi SN, Anand N, Dhawan BN. Evaluation of local anaesthetic activity of 4-N-butylamino-1,2,3,4-tetrahydroacridine hydrochloride (centbucridine)—A 4-substituted polymethylenequinoline. Indian J Exp Biol 1982;20:327-9.
36. Patnaik GK, Dhawan BN. Pharmacological study of 4-N-butylamino-1,2,3,4-tetrahydroacridine hydrochloride (centbucridine)—A new local anaesthetic agent. Indian J Exp Biol 1982;20:330-3.
37. Bhakuni RS, Singh T, Kahol AP, Tewari A, Tandon S, Khanuja SPS, Inventors. Single pot conversion of artemisinin into artemether. US

Patent No. 6,683,193 B2, January 27, 2004. https://patents.google.com/patent/US6683193B2/en
38. Bhat BK, Seth M, Bhaduri AP. Recent developments in 8-aminoquinoline antimalarials. Prog Drug Res 1984;28:197-231.
39. Dutta GP, Puri SK, Bhaduri AP, Seth M. Radical curative activity of a new 8-aminoquinoline derivative (CDRI 80/53) against plasmodium cynomolgi B in monkeys. Am J Trop Med Hyg 1989;41:635-7.
40. Gandiha A, Marshall IG, Paul D, Singh H. Neuromuscular and other blocking actions of a new series of mono and bisquaternary aza steroids. Journal of Pharmacy and Pharmacology 1974;26:871-7. https://onlinelibrary.wiley.com/doi/abs/10.1111/j.2042–7158.1974.tb09195.x
41. Wikipedia contributors. (2020, June 21). Candocuronium iodide. In Wikipedia, The Free Encyclopedia. Retrieved January 18, 2021, from https://en.wikipedia.org/w/index.php?title=Candocuronium_iodide&oldid=963741582 [Last accessed on Jan 18, 2021].
42. Nagarajan K, Arya VP. Two Decades of Medicinal Chemistry Research in India. J Scientific & Ind Res 1982;41:232-40,- http://repository.ias.ac.in/93421/1/139p.pdf
43. Wikipedia contributors. (2020, December 3). Nitroxazepine. In Wikipedia, The Free Encyclopaedia. Retrieved January 24, 2021, from: https://en.wikipedia.org/w/index.php?title=Nitroxazepine&oldid=992031527 [Last accessed on Jan 24, 2021].
44. Wikipedia contributors. (2016, September 23). Amoscanate. In Wikipedia, The Free Encyclopedia. Retrieved September 18, 2020, from: https://en.wikipedia.org/w/index.php?title=Amoscanate&oldid=740763096 [Last accessed on Sep 18, 2020].
45. WO2003009841A1-Novel pyroles having hypolipidemic hypocholesteremic activities, process for their preparation and pharmaceutical compositions containing them and their use in medicine. International filing date: July 25, 2002 [Inventors: Lohray BB, Lohray VB, Barot KG, Raval SK, Raval PS, Basu S]- https://patents.google.com/patent/WO2003009841A1/en
46. Saroglitazar magnesium | C50H56MgN2O8S2 – PubChem.https://pubchem.ncbi.nlm.nih.gov/compound/Saroglitazar-magnesium
47. Saroglitazar | New Drug Approvals. https://newdrugapprovals.org/tag/saraglitazar/
48. Company - CytoTools- https://cytotools.de/company.html
49. CENTAUR PHARMACEUTICALS PRIVATE ... - Zauba Corp-https://www.zaubacorp.com/company/CENTAUR-PHARMACEUTICALS-PRIVATE-LIMITED/U24230MH1980PTC023291
50. Unii-39K3DB2N3F | Cl2O6 – Pub Chem. https://pubchem.ncbi.nlm.nih.gov/compound/Unii-39K3DB2N3F
51. CTRI. http://ctri.nic.in/Clinicaltrials/showallp.php?mid1=2083&EncHid=&userName=dpocl
52. Centaur Pharmaceuticals Launches for the First Time in the .... 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
53. Ghosh PK. Government's Policies and Growth of Pharmaceutical Industry in India 1947–2018: A Review. Discussion Paper 236, Jan 2019, pp1-76 (Research and Information System For Developing Countries-www.ris.org.in)-https://www.ris.org.in/government%E2%80%99s-policies-and-growth-pharmaceutical-industry-india-1947-2018-review
54. Drugs from Sea | Ministry of Earth Sciences. https://www.moes.gov.in/programmes/drugs-sea