Revisiting Novel Active Pharmaceutical Ingredients from India

Achievements and Future Challenges

RIS
Research and Information System
for Developing Countries
विकासशील देशों की अनुसंधान एवं सूचना प्रणाली

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by

Prasanta Kumar Ghosh

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Preface

Professor Sachin Chaturvedi

Director General, RIS

RIS has actively been engaged in conducting research studies in the sphere of pharmaceuticals and health care sector. The institute has brought out a number of publications in this regard and also organized a number of policy dialogues with participation of large number of stakeholder. The present Report "Revisiting Novel Active Pharmaceutical Ingredients from India: Achievement and Future Challenges" by Dr Prasant Kumar Ghosh is a valuable addition in our endeavor towards promoting research on health care sector.

The focus of the study is on issues related to new drugs discovery; New Chemical Entities (NCEs) and Novel APIs discovered in India; efforts made on Novel APIs by various actors since 1947. The study has also explored major generic drugs manufactured and exported from India and initiatives by the Indian Government for promoting R&D on novel APIs. The study highlights that though India has a well-developed pharmaceutical industry, the third largest in the world in terms of volume of production and tenth largest in value, the area requires huge R&D investment for fostering new approaches.

The study calls for setting up of an independent Novel Drug Development Authority for conducting research and translating the outcome into applications. It also suggests that development of novel APIs should be part of the work programme of newly established National Research Foundation (NRF).

I compliment the author of the study Dr Prasant Kumar Ghosh, who has a background of hands-on experience in research and development, production and administration of drugs and pharmaceuticals, diagnostics and clinical chemistry reagents of 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.

I am sure the study would serve as an important reference for policy makers, academics, practitioners and other stakeholders.

Sachin Chaturvedi

Executive Summary

Abstract: The discovery of novel active pharmaceutical ingredients (APIs) is ardent, time-consuming and expensive. India has a well-developed pharmaceutical industry, which is considered to be the third largest in the world in terms of volume of production, and tenth largest in value. In the allopathic system of medicines, about 5000 numbers of APIs have been invented thus far and presently about 3000 are being used for the treatment, mitigation and cure of all kinds of human ailments and human diseases. India has discovered only 16 novel APIs, of which only six are presently available in the market. In order to remain globally competitive and dominant, India has to steer and to foster newer approaches. Some suggestions towards these ends have been made.

Worldwide new drug discovery in the arena of defined and well-characterised small and large molecules is fundamentally and inherently an intense search for new compounds for treatment of different types of diseases and ailments. New drugs were discovered earlier mainly through chemical synthesis although active ingredients have also been isolated from plants and plant-parts. Presently drug discovery research has undergone a sea-change and several newer tools and computation methods have been integrated into the work plan. With the advent of modern biotechnology, multiple newer methods have come into practice. India had been involved in the search of new chemical entities to be used as novel active pharmaceutical ingredients (APIs) for several decades, starting from early years of 1900. However due to various constraints, the progress had been hampered up to late 1960s. In the meantime, the Indian government after independence deliberately took steps to remove the legal hurdles of manufacture by amending the earlier Patents act by instituting Indian Patents Act 1970, whereby the new Act abolished product patents for pharmaceutical active ingredients and there was a sea change in the scenario. Indian entrepreneurs came out with innovative new processes for the manufacture of a wide range of already known active pharmaceutical ingredients .The period from early 1970s to the decade of early 2000s enabled the development of great skills in handling of varied chemical reactions by developing innovative processes. In the meantime, from the early years of pre-independence up to the present time a small number of dedicated individuals, institutions and groups kept them engaged into the development of innovative new APIs. It is their efforts that a small number of new drugs were invented / discovered from India.

Efforts were carried out for the discovery on new drugs in the government-owned Indian institutions and public sector units; multinational companies; as well as the Indian private sector companies. Among the government-owned Indian institutions and public sector units , mention needs to be made of the British-established Campbell Medical College, Calcutta (later renamed as Nilratan Sircar Medical

College & Hospital, Kolkata); Regional Research Laboratory, Hyderabad (later renamed as Indian Institute of Chemical Technology (IICT), Hyderabad; All India Institute of Medical Science (AIIMS), New Delhi; Hindustan Antibiotics Ltd, Pimpri, Pune, Maharashtra; Central Drugs Research Institute, Lucknow; and Punjab University , Punjab. A number of other national institutes have also been engaged in such efforts significant among these are the Regional Research Laboratory, Jammu (renamed as Indian Institute of Integrative Medicine in 2007); Indian Institute of Chemical Biology, Kolkata; Institute of Microbial Technology, Chandigarh; and some others. No new API has yet been discovered by these institutions however.

Among the multinational companies mention must be made of the efforts carried out at Ciba-Geigy Research Centre, Bombay; Hoechst Research Centre, Bombay; Smith Kline and French, Bangalore; Astra-IDL Ltd, Bangalore; Boots India Ltd, Bombay; and certain others.

Among the Indian private sector industries, significant efforts were made by several companies for the development of cost-effective technologies and to manufacture a host of generic APIs. A number of such companies later became poorer while several others emerged during the recent times.

Studies have been made on the operating abilities of sixty different Indian companies, selected from all over India, keeping in view the sizes and operating endeavor, man-power deployed, generic products manufactured and regional distribution.

It was revealed that the Indian API manufacturers had not paid much attention to the development of novel APIs. It is already known that the development of novel APIs are time consuming, the efforts are extremely costly and bear high financial risks. The chances of a successful outcome are very low. The business environment in India has been extremely competitive and the profit-margins from manufacture have been low, which did not ensure generation of sizable surpluses for deployment in R&D for such purposes, although if a jackpot drug could be discovered and introduced in the global market, the returns would be very high till the time the novel APIs are protected by strong IPRs .It requires to be explored what policy intervention could have been made and what business environment could be created at national level to enthuse the Indian industry to invest and concentrate on the development of novel APIs.

There are also a sizable number of other units involved in the manufacture of drugs using modern recombinant DNA (r DNA) technologies. These companies are also involved in R&D. However, in this study information on discoveries of drugs based on use of r DNA technologies are not dealt with.

The number of new chemical entities used as novel APIs which were discovered in India were only 16; these were Urea stibamine; Methaqualone; Enfenamic acid; Hamycin; Centimizone; Centbutindole; Ormeloxifene; Centpropazine; Centbucridine; alpha, beta-Arteether ;Bulaquine; Chandocuronium iodide (INN) [formerly known as Chandonium iodide, HS-310] ; Nitroxazepene[Brand name Sintamil] ; Amoscanate (INN),[also known as Nithiocyamine]; Saroglitazar (INN) [Trade name Lipaglyn]; and Diperoxychloric acid [Trade name of formulation WOXheal]. A novel cardiac glycoside by the name Peruvoside was discovered in India; it was isolated from matured fruits of ThevetianerifoliaJuss . Gugulipids, another novel active substance, were extracted and isolated from Guggul, an oleoresin which is obtained by tapping and injuring the Commiphoramukul tree. Another pharmaceutically active extract, known as the Bacosides, which are dammarane-type triterpenoid saponins was isolated from Bacopa monnieri, a medicinal Ayurvedic herb which has been in use in Indian syatem of medicine to sharpen intellect and attenuate mental deficits. Consap, another novel product

from India is a sterile contraceptive cream produced from the saponins obtained from soap nuts of the plant Sapindusmukorosii (commonly known as Reetha in NorthIndia). DalZbone, a novel substance, is a product developed from the leaf extracts of Sheesham tree (Dalbergiasissoo). Among the 16 novel synthetic APIs mentioned above, formulations based on the six APIs namely Ormeloxifene or Centchroman ; alpha, beta-Arteether ; Bulaquine, Nitroxazepine; Saroglitazar; and Diperoxychloric acid are available in the market in February 2021. Novel APIs mentioned here are well-characterised new chemical entities and do not include inadequately characterised pharmaceutical ingredients including mixtures and extracts from plants or animal sources, modern biotechnological drugs, cellular and gene therapies, etc.

The discovery of a number of novel APIs is no doubt a remarkable achievement for India. These happened from the strong commitment and devotion of a small number of outstanding scientists who played the key role to discover and invent. For a country of Indian magnitude, the number of novel APIs discovered is however, quite small. It is necessary to ponder why India could not become a leading nation among the world leaders in new drug discovery arena.

India has been manufacturing a wide range of generic APIs and making these available for consumption in India; many of these are also being exported at cost-competitive prices. According to the estimate of the author, presently about 2200 numbers of generic APIs are being utilised in Indian Pharmaceutical Industry for the manufacture of generic and branded formulations. Of these 2200 generic APIs, about 1000 numbers are being manufactured in India while the rest are being imported and used. Of the 1000 numbers of generic APIs, nearly 600 numbers manufactured in India are also being exported, which activity enables the country to earn sizable foreign exchange, The turnover of the Indian pharmaceutical industry during 2018-'19 was reported at INR 258534 crore (US$ 36.933 billion at conversion of 1 USD= 70 INR); the imports were INR 34944 crore (USD 4.992 billion) comprising of bulk drugs, drug-intermediates and small quantities of finished formulations but excluding medical devices; the exports of all medicines was at INR128028 crore (USD 18.29 billion) of which generic bulk drugs exports was INR 26886 crore (USD 3.84 billion). The Indian pharmaceutical industry turnover of US$36.93 billion during 2018-'19 was about 3% of the global turnover of pharmaceutical industry(estimated at US$ 1227.6 billion during 2018-'19). The Indian vaccines industry, during the same period attained a production turnover of US$1.48 billion, which was about 4% of the global total turnover of vaccines (estimated at US$ 35.2 billion) during the period , and was also about 4% of its total turnover of pharmaceutical industry in the country. Indian vaccines industry production turnover was only about 0.12% of the total global turnover of the pharmaceutical industry.

The country has acquired commendable expertise in the handling and manipulation of complex chemical reactions, which in itself is a great achievement. It is surmised that if India could come up with new chemical entities which are to be used as novel APIs, India shall be able to come out with innovative industrial manufacturing methods using the present skills at cost-competitive ways. Since India is not yet a hub for the discovery of novel APIs, every effort needs to be made that India uses the synthetic, engineering and managerial skills for large-scale production of novel APIs. The moot question is why India should be lagging behind.

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 individual wealth. It has been suggested that in order to enable India to acquire competence in the discovery of novel APIs, a national effort is

called for. It is considered prudent to set up a new establishment like an independent Novel Drug Development Authority which should have infrastructure for the conduct of research and provisions for translation of research results into applications. Such an authority should be under the direct supervision of the Minister for Science & Technology/Prime Minister. The mission, objectives, aim, infrastructure and budget of such an establishment/authority have been discussed.

The recent budget announcement of the Finance Minister on February 01, 2021 to earmark INR 50,000 crore (US$ 7.143 billion) over five years for the creation of a National Research Foundation (NRF), which shall be an umbrella body that is expected to fund research across a range of disciplines, from science and technology to humanities is an announcement of great vision. Development of novel APIs need to be an important discipline and task, which can be a part of the NRF to steer and to foster India to move ahead in the path of discovery of novel APIs.

I
Introduction

India has presently more than 3,000 pharmaceutical companies **[1]** with a network of over 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 our estimate, the number of generic active pharmaceutical ingredients [APIs] which are presently being manufactured in India is about 1000, of which about 600 are significant ones with high export potential while the finished pharmaceutical formulations sold in India include total of about 2200 APIs. About 1200 numbers of bulks generic APIs are imported and used for the manufacture of finished formulations. Several of these 1200 generic APIs were being manufactured in India earlier, especially before 1991.In terms of high value turnover, these included the fermentation-based antibiotics, sulpha-drugs, several synthetic analgesics and vitamins among others. In the present policy environment, imported formulations of about 30 IPR-protected medicines are also sold in India. It is estimated that from the time of the beginning of the seventeenth century, when Pharmacopoeia began to be used for the allopathic system of medicines, the number of active pharmaceutical ingredients used by the human for the manufacture of human medicines would not be more than 5000 in numbers and that presently, the world over about 3000 APIs are being used for the treatment, mitigation and cure of all kinds of human ailments and human diseases.

The turnover **[2]** of the Indian pharmaceutical industry during 2018-'19 was reported at INR 258534 crore (US$ 36.933 billion at conversion of 1 USD= 70 INR); the imports were INR 34944 crore (USD 4.992 billion) comprising of bulk drugs, intermediates and small quantities of finished formulations but excluding medical devices; the exports of all medicines was at INR128028 crore (USD 18.29 billion) of which generic bulk drugs exports was INR 26886 crore (USD 3.84 billion). Indian pharmaceutical industry is considered to be the third largest in the world in terms of volume of production, and tenth largest in value. The Indian pharmaceutical industry turnover of US$ 36.93 billion during 2018-'19 was about 3 per cent of the global turnover of pharmaceutical industry(estimated by the author at US$ 1227.6 billion during 2018-'19). The Indian vaccines industry, during the same period attained a production turnover of US$ 1.48 billion, which was about 4 per cent of the global total turnover of vaccines (estimated at US$ 35.2 billion by the author) during the period, and was also about 4 per cent of its total turnover of pharmaceutical industry in the country. Indian vaccines industry production turnover was only about 0.12 per cent of the total global turnover of the pharmaceutical industry.

There are over 2700 generic API manufacturers in India, of which majority are in the small scale sector. The Indian API manufacture in value terms was about 8 per cent of the value of global API market in 2016-17.The APIs manufactured in India are accepted globally because of their internationally acceptable higher quality standards **[3].**These facts indicate that India

has generated competence in complex chemical synthesis; hold in innovative processes and deployment of low cost skilled manpower, which are 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 come out with multiple numbers of novel APIs too. However, the number of new chemical entities [NCEs] approved and used as novel APIs from India were only 16 in numbers, which included Urea stibamine; Methaqualone; Enfenamic acid; Hamycin ; Centimizone; Centbutindole; Ormeloxifene; Centpropazine; Centbucridine; alpha, beta-Arteether ; Bulaquine; Chandocuronium iodide (INN) [formerly known as Chandonium iodide, HS-310]; Nitroxazepene[Brand name Sintamil] ; Amoscanate (INN),[also known as Nithiocyamine]; Saroglitazar (INN) [Trade name Lipaglyn]; and Diperoxychloric acid [Trade name of formulation WOXheal]. Certain other novel discoveries of APIs which were not synthetic but which were isolated from plant sources were Peruvoside **[4,5]**, a cardiac glycoside which was isolated from matured fruits of ThevetianerifoliaJuss; Gugulipids extracted and isolated from Guggul, an oleoresin obtained by tapping the Commiphoramukul tree; Bacosides which are dammarane-type triterpenoid saponins isolated from Bacopa monnieri, a medicinal Ayurvedic herb which has been in use in Indian system of medicine from ancient time 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 NorthIndia); and DalZbone a product developed from the leaf extracts of Sheeshamtree (Dalbergiasissoo) **[6]**. Among the novel 16 synthetic APIs, discovered in India, formulations based on the six APIs, namely Ormeloxifene or Centchroman(Trade names of formulations: Chhaya, Saheli, Novex-DS, Centron, and Sevista**[7]**; alpha, beta-Arteether(Trade name of formulations :E-Mal)**[8]**; Bulaquine (Trade name of formulation sold with chloroquine : Aablaquine) **[9]**; Nitroxapine(Trade name :Sintamil) ; Saroglitazar (Trade name of formulation :Lipaglyn) **[10]** ; and Diperoxychloric acid (Trade name of formulation WOXheal) are presently (2021-February) available in the market. These products are from CSIR-CDRI, a National Laboratory; from a foreign multinational company [MNC]; and from an Indian MNC respectively. The other products invented in India such as Enfenamic acid; Centimizone; Centbutindole; Centpropazine; Centbucridine; and Candocuronium iodide were marketed by certain Indian companies who had procured the technology from CSIR-CDRI **[6]**, a National Institute and Punjab University. It appears that the Indian companies could not capture adequate market for these products in India. There are no indications in the literature if 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 **[11]**, 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 study, efforts have been made to assess what newer innovative steps 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 Study

The intent of the study is to focus on the Indian discovery of new chemical entities (NCEs), which have been discovered and used as new and novel APIs (together with their formulations) as new pharmaceutical formulations. Intent of research work carried out for the development of new APIs, which are chemically well-characterised, has been described. This area requires massive

R&D investment. Indian research in this area is yet quite small 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. Search had been made for the new chemical entities which have found use as new active pharmaceutical ingredients (APIs) developed in India for the first time in the world and which have been later formulated and approved as usable pharmaceutical formulations for human use.

In the Indian context of new drug discovery, it needs to be mentioned that within the limited and lesser access to resources, a number of noteworthy developments took place, which emanated especially from the zeal and devotion of a small number of outstanding researchers and scientists. Special mention need to be made of the developments that took place from 1950s and thereafter when certain government–run organisations 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 discovery of new drugs as has been described briefly.

In an endeavor of searching the NCEs discovered by the Indian scientists, it was considered prudent to assess in brief the pathways that have been followed the world over towards such aspirations and how the pathways have evolved over time. Thereafter, the Indian discoveries have been narrated. The major Indian efforts in the manufacture of generic APIs have also been assessed to ascertain the expertise that has been established in the country. Following this, the gap in the development of novel APIs have also been critically examined and some suggestions have been made for bridging the gaps so as to enable India to emerge as a major player in the discovery of novel APIs.

Methodology of the Study

While conducting the study, information was gathered from the web sites of all Indian institutes and universities as also from the multiple papers and pages existing on the internet. Google search engine was used. The websites of more than sixty API manufacturing units were also consulted in considerable details. In addition, the web sites 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 and referred to for seeking information.

II

New Drug Discovery: Methods, Approaches and Issues

Worldwide new drug discovery in the arena of small and large molecules is fundamentally and inherently an intense search for new compounds for treatment of different types of diseases. Such compounds are essentially organic but could be inorganic too. Numerous compounds are synthesised and their properties are measured towards their efficacy to treat human diseases. Only a small fraction of the new compounds continuously searched for, which originate by isolation from natural substances such as plants or animals; or chemically synthesized; or produced by recombinant DNA (r DNA) technology, demonstrate activity against specific diseases or disabilities. Over the years, the disease pattern of societies has also changed. The present day world is on the lookout for finding effective compounds that are useful for treating various diseases of which chronic diseases like cancer, arthritis, cardiovascular diseases, diabetes and several viral diseases like HIV, HBV, and HCV among others continue to remain a major health problem worldwide **[12-13]**. Co-infection from HIV and HBV has been a leading cause of liver disease resulting in worldwide morbidity during the last three decades **[14-15]**. Several newer viral diseases **[16]** caused to human such as Crimean-Congo hemorrhagic fever, Ebola, Middle East respiratory syndrome coronavirus, Severe Acute Respiratory Syndrome , Lassa fever, Nipah virus, Rift Valley fever, Chikungunya, severe fever with thrombocytopenia syndrome and Zika virus are looming closer; effective medicines are yet to be in place for undertaking effective treatment. A large number of tropical diseases are impacting the health of people in the developing countries **[17-19]**; these diseases include tuberculosis, malaria, sleeping sickness, dengue, leishmaniasis, Chagas disease and certain tropical ulcers such as Buruli uncer. Of late infection and death from Nipah virus had created considerable concern **[20-21].**Presently, the pandemic created by the RNA virus SARS-CoV-2 has caused unpredicted distress to people almost in every country of the world **[22]** and India **[23]** is no exception.

Several of the currently deployed drugs to treat chronic diseases are very toxic, have low half-life and often acquire resistance thereby necessitating the physicians to look for a change-over to other less toxic and more effective ones. New drug discovery, therefore, requires the researchers to constantly invent and discover new chemical entities that are more effective, less toxic and which do not easily acquire resistance to the treatment process. New drug discovery requires besides expertise in chemical synthesis, profound knowledge of understanding the mechanism of drug action on target cells or components of cellular machinery such as the peptides, proteins and nucleic acids such as DNA and RNA and certain other macromolecules. Once the drug target is identified and an assay method is developed on how the target in the cellular model is modulated by the candidate compounds, synthesis of a wide range of

compounds is undertaken; these are tested in cellular model and then on an animal model, if available. Simultaneously, the active ones are evaluated for toxicity and the competent ones are formulated and used in clinical trials in various phases. The most effective ones are picked up for manufacture after the regulatory approvals are obtained. In the meantime, the novel compounds are protected by appropriate laws on intellectual property rights (IPR). A wide range of expertise is required to enable the discovery of new drug molecules and new methods of treatments.

Earlier new drugs were discovered by using traditional drug discovery techniques. Traditional techniques involve search for active ingredients in and from natural sources; random screening of new chemical entities produced by chemical synthesis; trial and error method of using multiple new synthetic compounds or products isolated from natural sources; accidental discovery; and even through the ethnopharmacological approach based on integration and utilisation of several disciplines such as chemistry, botany, pharmacology and others. These techniques were used earlier 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 **[24-26]**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 specialising in the use of highly sophisticated instruments, biologists, pharmacologists and clinicians with profound knowledge in medicinal chemistry. They also create access to expertise in r DNA technology for the synthesis of biological entities for use as drugs wherever r DNA –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 the 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 behaviour 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 utilises 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. 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 effect a change in the biological target molecule **[27] .**

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 over binding 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, which are discovered, have the advantage of being more efficacious with prolonged therapeutic effects, thereby requiring lesser dosing and is considered as 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 **[28-30]**.

The drugs which have been approved by the statutory authorities act on one or more of the protein targets **[31]**; such protein targets are of various kinds such as G protein-coupled receptors **[32]**; enzyme inhibitors **[33-35]**including especially protein kinases, proteases, esterases, and phosphatases; ion channels **[36]**including ligand-gated ion channels and voltage-gated ion channels; nuclear hormone receptors **[37-38];** structural proteins **[39-40]**such as microtubule/ tubulin membrane; and several transport proteins **[41-42]**.There are also a number of drug targets in the nucleic acid category **[43-44]** .

An updated data bank exists in the public domain from 2018, known as Drug Bank 5.0. This data bank includes information on pharmacometabolomics which is the part of science that analyses and quantifies the metabolites existing in a biological material; levels of gene expression; as well as protein expression levels. These data base can serve as an excellent starting point for multiples of areas of novel drugs discovery research. According to these data base, there exists more than 4560 numbers of drug targets **[45]** 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 (QSAR). QSAR methods can be described as the application of machine learning **[46]** 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 the 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 assemblance 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 programmes are used to determine the binding affinities.

In both the ligand-based drug designing and structure-based drug designing computational knowledge is essential and novel compounds can be designed and synthesised. The novel compounds are then evaluated in cellular or animal model and investigations would proceed further **[47]** .

Utilising 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 so as to reduce the overall costs. High-end computer specialists having considerable knowledge in medicinal chemistry and biology are required to be inducted in the team.

There are several proprietary drug discovery platforms which have evolved over the recent years, and which models are intelligent combinations of the above with added additional features. For example, the Smart Cube **[48]** technology combines robotics, computer vision, machine learning and bioinformatics all together, to capture and analyze information and data to enable the evolution of behavioral phenotypes of novel compounds or for disease model pathways. The machine learning methods supplement the existing knowledge on the phenotypic drug discovery platform. The success of the phenotypic approach is eventually dependent upon unveiling the molecular mechanism of action of the new molecules isolated/invented. Towards these efforts, the machine learning methods supplement the knowledge.

Drug discovery is indeed a complex process requiring the mounting of multiple experiments at different times as one makes progress. After a discovery team is formed and the infrastructure for implementation is in place, investigation starts on understanding the disease and identifying the targets which through various physico-chemical and/or biological modulations manifest the disease. In earlier paragraphs the nature of the targets and their modifications have been discussed. Once the targets are identified and the modifications that take place in disease conditions that can be measured either in the animal model or in the single-cell model with assay methods for measuring the modifications are established, every new chemical entity can be assessed and their scores measured. In the meantime, one group continues to synthesise or isolate new chemical entities and make these ready for assessment. Idea about the structure of the new chemical entity to be synthesised can evolve not only from the structures of already-known active compounds but also from the inputs from the machine –learning predictions **[49]** . The issue at this stage is to accurately identify the target and evolve accurate methods to assess the scores of NCEs. If proper animal models are not used at this stage of evaluation and if the assessments are based on in-vitro assays using single cell-lines, then there are immense possibilities of discarding many of the identified NCEs later; this would happen at the stage of re-evaluation of the selected NCEs in proper animal model.

However, if the number of NCEs to be evaluated are very large, then in-vitro model of using single-cell-omics are desirable as these evaluations cost much less and require much less time to evaluate. A single-cell is the fundamental unit of tissues with homogeneity in genetic make-up although heterogeneity is manifested with time (age), three-dimensional positioning and space available in the tissue architecture. Moreover, the behaviour of single cells of a tissue in terms of intercellular and intracellular interactions as also response to changing environmental conditions is not adequately understood yet. Therefore, if simultaneously multiple single-cells are concurrently studied, each at the single-cell level, a study referred to as the single-cell- omics, much information can be gathered which are useful for new drug discovery. The term "cell-omics" denote and include new sets of technologies that aim at identifying, characterising and quantifying at single-cell level its genomic sequences, deciphering gene-exome sequencing thereby understanding protein-coding portion of the genomic DNA(also termed as exomics), unveiling RNA transcripts, determining and characterising translated proteins and studying the metabolites expressed at single- cellular level. Better understanding can evolve if single-cell genomics, exomics, RNA transcripts, proteomics and metabolomics are studied exhaustively.

In this context, it needs to be mentioned that towards accurate bioassays at single-cell level or at tissue level or even at organ level, the miniaturisation of assay procedures has been contributed by the novel development of multiple numbers of lab-on-a-chip technologies. Dimensionally, in these techniques, very small volumes in the range of 10^{-9} to 10^{-18} liters of fluids with channels of dimensions of 10 to 100 micrometers are used. High quality affinity reagents are required for accurate measurements. These technologies, also known as microfluidics, have enabled precise and meticulous modeling of physiological and biological conditions in tininess and compactness for research enabling testing of various aspects of drug discovery.

In chronic diseases, as also in diseases manifested over time and emanating from malfunctioning of organs and tissues, heterogeneity arises in single-cells in tissues that are diseased. This is mainly due to acquired heterogeneity in the newer born cells at the levels of genes, integrated over-all functions of tissues and compositional fronts. Because of acquired heterogeneity, there would be complexities in the understanding of the effects of drugs on the tissues. In studying complex chronic diseases especially in various types of cancer, the establishment of animal models becomes difficult. In such problems, studies at single-cell level at single-cell-omics level become more useful in developing new drugs. Since multiple malfunctioning at tissue level are anticipated at individual single-cell level in the diseased tissues, the effective drug regimen would be a combination of drug-molecules, each one acting at different events. It is anticipated that one drug would not be able to arrest the malfunctioning which is perceived as an integrated outcome, originating from multiple diseased cells in multiple ways. Here again, as there would be variations among the genetic make-ups in each individual , effective treatment options are anticipated to vary in usage-choice as well as in quantities deployed, from person to person. Obviously before applying such drugs or drug-combinations on individuals in phase studies, evaluation in proper animal model would be required after completing the evaluation in single-cell-omics model.

For more information in this area, several useful references are cited **[50-57]** .

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.

Novel drugs discovery in industry is presently driven by economic considerations and those areas of problems are chosen where the monetary returns are very high. Academic institutions are, however, driven by challenging problems and,

therefore, research for new drug discovery in such institutions address more of the scientifically challenging problems. Consequently, depending upon the actors, the focus of research gets modulated. Research problems identified at national levels again depend upon the health priorities of nations, disease preponderance, funds availability and many other regional considerations.

New Drugs Discovery in India: the Actors

The Indian companies have concentrated in general, on the development of modern pharmaceutical formulations in the Allopathic system, using already available active pharmaceutical ingredients (APIs). As India is also known to be using a wide range of traditional medicines described in a multiple number of traditional treatment system 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 own API manufacturing facilities wherefrom the APIs produced are either used for in-house consumption or are being sold to other buyers including the importers. The APIs manufactured are generally falling within the category of generic drugs. Several companies in India have also developed innovative new combinations of generic APIs as also pharmaceutical formulations of better types by regulating the delivery mechanism of the active ingredients. Use of such formulations requires generation of information in animal model for safety and efficacy followed by generating clinical data on human subjects. As a result, establishments and facilities for pre-clinical and clinical research have also come up in the country.

Novel synthetic methods of known APIs is essentially an effort which took roots in India in late 1960s and especially during the decade of 1970s after the Indian Patents Act 1970 was promulgated, which 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 non-availability of adequate trained man power, the research for the synthesis of known drugs was moving at a snail's speed. The then Indian Parents 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 were also deemed to be protected as per the law. Availability of petrochemicals-based raw materials was scarce due to the non-availability of petrochemicals-based industry. The organic raw materials were based on coal-tar fraction-based products which were scanty in availability and were expensive too. The fermentation –based ethyl alcohol, which served as the starting materials for many active substances, synthesised 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 early fifties (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, there had been visible great progress in the medicinal chemistry research in India. Efforts were made primarily through chemical synthesis to invent non-fringing 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 towards discovery of novel APIs. Certain diseases especially endemic to the tropical climates were especially concentrated upon. The

therapeutic areas chosen were development of novel anthelmintics (against hookworm, round worm , 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 a phenomenal growth and became an organised, 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 pharmaceutical formulations manufacturing industry. India is presently the largest supplier of generic drugs globally. APIs are the largest segment of Indian pharmaceutical market. APIs are synthetic chemical entities (including the high potency active pharmaceutical ingredients) as well as the biotech APIs. This study is all about APIs originating from chemical synthesis. Biotech-based drugs produced by deploying r DNA technology and others evolved from other biotechnology methods are not discussed here.

It is worth mentioning here that biotechnology based drugs and pharmaceutical formulations using recombinant DNA technology is another area, where India has invested considerable sum from the decade of 1990 onwards, to develop biosimilar products (also called as similar biologics). Here also the pharmaceutical formulations developed are mainly for products which are already known. Use of recombinant DNA (r-DNA) technology, also described as genetic engineering (GE) technology the world over, started from the time the fundamentals of the molecular cloning of foreign DNA into plasmids (bacterial extra-chromosomal DNA elements) were understood during the early 1970s. With further development in the knowledge base in r DNA technology, the techniques were extended to mammalian cells in early 1980s when transgenic proteins could be expressed in such cells. These developments brought about a revolution in the production of bioactive therapeutic proteins in transgenic bacterial hosts and mammalian cell lines, resulting in the production of a multiple number of therapeutic proteins for human use. Another technology by the name hybridoma technology discovered in 1975, which enabled the creation of "immortal" hybrid cells by fusing normal B cells from immunized mice with their myeloma cells was another landmark invention; by the use of this technology with further refinements over the years, this enabled the development of humanized monoclonal antibodies. Designed monoclonal antibodies could be used to intervene multiple complex molecular and cellular interactions , thereby arresting several defects and disease syndrome in human.

The waves of these developments also entered into Indian arena. Already invented and described therapeutic proteins produced by the use of rDNA technology as also designed monoclonal antibodies approved for use in human therapy elsewhere began to be produced in India after the Intellectual Property Rights on such products expired. However, very few Indian companies invested in these areas for the development of new therapeutic molecules. In the meantime, advancements in modern biotechnology continue and presently certain virgin areas such as development of DNA and RNA vaccines and newer adjuvants to intensify their efficacy are being researched upon. Other newer areas are the development of cellular and gene therapies, using r DNA technology are also progressing fast . In these areas, Indian research is yet insignificant. In an elaborate review, the author in 2016 had published a paper which had depicted the approval of 34 similar biologics, also termed as biosimilar products , which were approved for marketing in India.[Ghosh P K.,

Similar Biologics: Global Opportunities and Issues, J Pharm Pharm Sci (www.cspsCanada.org) 19(4) 552 - 596, 2016 552- https://pubmed.ncbi.nlm.nih.gov/28057166/]. These covered all the recombinant DNA products including rDNA vaccines, therapeutic bioactive proteins and monoclonal antibodies. These areas are flagged as they are significantly contributing to the excellence of Indian pharmaceutical industry in the manufacture of IPR-expired biotech substances.

III

New Chemical Entities and Novel APIs Discovered in India

The novel APIs discovered in India are placed in Table-1.

Urea Stibamine

The allopathic system of medicines was introduced in India through the 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 & 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 the late 1800 AD. Development of vaccines was considered to be the best option at that time than any other option for winning over the diseases. As a consequence, 15 vaccine institutes **[93]** were established by the British rulers. The establishment of these institutes in the beginning of 1890s ushered the modern medical research in the country.

During the prevailing environment existing in these early years of 1900 AD, researches in chemotherapeutic substances were difficult to carry out. The German scientist Paul Ehrlich's idea **[94]** of "magic bullets" proposed in 1900 AD could not be pursued by the then government because of various constraints and indeed were 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 **[95]** that just like when a gunshot is made, propelling a bullet to hit a specific target, so also there could be chemicals which could be used to specifically target the invading microorganisms. In 1909, this concept of 'magic bullet' was also established and elaborated by Ehrlich himself by his discovery of Salvarsan**.** Salvarsan was used for the treatment for syphilis and trypanosomiasis (sleeping sickness).The drug was introduced at the beginning of the 1910. This was an organoarsenic compound. Another name of Salvarsan is Arsphenamine **[96]**. Because of the constituents of the compound containing arsenic, this was found to be substantially toxic to human and was later discontinued. However, during the prevailing time this was an outstanding contribution to human kind.

The researchers in early years of 1900 AD could not easily pursue investigations in chemo-therapeutic substances in India. From the study of the various contemporary literatures the author felt that this was essentially because of scarcity of starting chemicals, inadequate research infrastructure and less advancement in the pursuit of chemical synthesis. Raw materials were essentially inorganic in nature. But yet from India there was a man who, utilizing the available chemicals during early 1900s started synthesizing new chemical entities to treat leishmaniasis. His

name was U. N. Brahmachari who was a medical doctor and a chemist too by qualifications. After Paul Ehrlich, U. N. Brahmachari was the second person who developed a synthetic drug to treat visceral leishmaniasis. He synthesised several compounds **[58]** and tested those in his lab and then came up with his discovery. And his discovery can certainly be considered as the second "magic bullet", a great feat in the history of drug research.

After Paul Ehrlich, it was the Indian scientist U.N. Brahmachari who made the seminal discovery of Ureastibamine to treat leishmaniasis. During those periods in 1920s and 1930s, many deaths were caused in India, especially in the tea gardens, due to *Leishmaniadonovani*, the causative organism of Kala-azar. U. N. Brahmachari began his research in Kala-Azar in early 1920s in collaboration with Colonel Sir Robert Neil Campbell. Earlier, in 1901 he received a teaching position in Physiology in Dacca Medical School and was a blue eyed Indian to Sir Gerald Bomford who offered Brahmachari the position. U.N. Brahmachari had an illustrious academic career. He obtained his Doctor of Medicine Degree in 1902. He also had a PhD in Physiology in 1904, which degree he acquired by working on the physiochemical properties of red blood cells. Earlier, Brahmachari obtained his M Sc degree in Chemistry from the Presidency College in 1894 and his BA in Mathematics in 1893 from Hooghly College. He topped the BA examination and was awarded the Thwaytes Gold Medal! He was all along a brilliant student **[97]**.

The research lab in the then Campbell Medical College, Kolkata of U. N. Brahmachari was not glamorous. The then Campbell Medical College is now known as the Nilratan **[98]** Sircar Medical College & Hospital - [NRS], Kolkata. Various writings on Brahmachari show that his lab did not have electricity and therefore when Brahmachari had to work at night, he had to use a kerosene lamp. The lab did not have even a wash basin. His main equipments were a microscope and lab appliances to synthesize, purify and characterise chemical entities by heating, boiling, distilling, cooling and the like. And yet with meager facilities, Brahmachari started synthesizing and investigating new chemical entities (NCEs) on *Leishmaniadonovani* in his lab watching the effects of his NCEs on the organism in cultured media under the microscope! Since he had a chemistry background and since he was a medical doctor himself, his interest in chemotherapy was natural. He synthesised several antimonial compounds. And eventually he found Ureastibamine which was the reaction product of para-aminophenylstibonic acid with urea. The product was para-aminophenylcarba moylaminooxystibinic acid or (4-aminophenyl)-(carbamoylamino) oxystibinic acid. This stable compound became the product of choice to treat leishmaniasis! This first modern synthetic drug, well characterised chemically was developed to treat visceral leishmaniasis in 1922 **[99]**. His medicine saved many millions of lives of poor people who used to get infected from the protozoal parasite, *Leishmaniadonovani.*

As soon as Urea Stibamine was discovered and introduced in India as a drug in 1922, the drug became the only drug of choice to treat the disease at that time. The drug was so efficacious that in 1923, the evaluators of the medicine wrote to the then Indian Kala-azar Commission,

"We consider that the value of urea Stibamine has been established as the most efficient drug at present for the treatment of Indian Kala-azar. The conclusion is based only on the experience gained in a series of cases, both Indian and European, which have passed through our hands or which have been treated with urea stibamine under our direction, a number totaling nearly hundred cases".

This was the deciding recommendations and, therefore, the drug was thereafter extensively used to treat visceral leishmaniasis in different parts of India and outside of India too. The drug saved millions of lives **[100].** The contributions of the drug in saving lives during those times are considered remarkable in the Indian history

The following Table-1 provides the list of NCEs and novel APIs along with pharmaceutical formulations developed there from in India.

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	Technol. transferred to industry and year of transfer	Whether in Indian market in January 2021	Remarks
1	Urea stibamine **[58-60]** [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 **[61-62]** [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 **[63-65]** [Analgesic]	CSIR-IICT	Sattur P B and Hashim R	1964	Transferred to Unichem Lab, Mumbai	No	Commercialized in 1981, but abandoned later
4	Hamycin **[66]** [Antifungal antibiotic]	HAL	Thirumalachar M J	1966	HAL manufactured and sold	No	HAL became sick & couldn't continue manufacture.
5	Centimizone **[67-69]** [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) **[70]** [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

Table 1 continued...

Table 1 continued...

7	Ormeloxifene (also known as Centchroman) **[71-76]** [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 **[6, 77, 78]** [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 **[6. 79, 80]** [Local anesthetic]	CSIR-CDRI	Patnaik GK, Rastogi SN, Anand N and Dhawan BN	1982	Technology transferred to Themis Chemicals Mumbai in 1987	No	Never marketed
10	alpha, beta-Arteether **[6, 81]** [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 **[6, 82, 83]** (Elubaquine) [Anti-malarial drug]	CSIR-CDRI	Bhat BK, Seth M, Bhaduri AP.	1984	Technology transferred to Nicolas Piramol, Mumbai in 1999	Yes	Available in market as Aablaquin (bulaquine and chloroquine combined as active ingredients)

Table 1 continued...

Table 1 continued...

12	**Chandocuronium iodide [6, 84, 85]** (now known as Candocuronium iodide) [Skeletal muscle relaxant]	Punjab Univ.and CSIR-CDRI	Gandiha A, Marshall IG, 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 **[86-87]**(Sintamil) [Antidepressant]	Hindustan Ciba-Geigy (taken over by Novartis)	Described by Nagarajan K and Arya VP	Before 1972	Product introduced in the market in 1982 by the Hindustan Ciba-Geigy	Yes	Being sold as Sintamil formulation
14	Nithicocyamine **[86,88]** (Amoscanate)	Hindustan Ciba-Geigy (taken over by Novartis)	Described by Nagarajan K and Arya VP	1976	Formulation approved by Indian Regulatory authorities in 1985	No	Markedly toxic for human use
15	Saroglitizar **[89-91]** [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	Cyto **[92]** Tools AG, Ger-many	Mark-Andre Freyberg and Dirk Kaiser	Centaur teamed up for co-development with Cyto Tools	Formulation marketed in India by Centaur in 2020	Yes	Marketed by Centaur under the trade name 'WOXHeal'

of medicines. This should also be considered to be an outstanding contribution to the knowledge of human medicines. But here also because of constituents used, the product was found to be quite toxic to human and was therefore discontinued later as better newer options became available.

In order to appreciate the magnitude of the discovery of Ureastibamine at that time, one has to visualise the period of 1920s; there was no effective drug in the hands of mankind to treat visceral leishmaniasis. Poor people were absolutely helplessly dying in different parts of the country.

It was a period when even Sulfa drugs (derivatives of sulphonamides) were not discovered. Sulfa drugs were discovered and introduced in 1935 by Gerhard Domagk **[101].** Penicillin was discovered in 1929 and was introduced in the market only in early 1940s during the World War II especially to treat the wounded soldiers. Penicillin G was the first chemically defined antibiotic which was produced from microbes and was used for treating human diseases. The medicine was the joint work of three pioneering scientists namely Alexander Fleming **[102]**, Ernst Chain **[103]** and H.W. Florey **[104]**.

On visceral leishmaniasis deaths, one can imagine what had been the status and environment of Indian drug research during the time of Brahmachari. The mentor of the author, (Late) Prof. (Mrs.) Asima Chatterjee while writing on U.N. Brahmachari, had remarked **[105]** about him as "Brahmachari was a genius but a maverick; a rebel". Indeed Brahmachari was an independent-minded person and an unorthodox, an unconventional, an unusual, an exotic individual! His invention was marvelous!

But the elite humankind had not adequately appreciated the work nor did they honour him adequately during his time or thereafter. Let us take note of the fact that Paul Ehrlich, Gerhard Domagk, Alexander Fleming, Ernst Chain, and H. W. Florey all got the Nobel Prize but not U. N. Brahmachari. Even India after independence had not adequately recognized this great saint. The Nilratan Medical College, Kolkata does not have any web page on its site, dedicated to this great man! A small street **[106]** in Kolkata was named after this man and in 2012, the CSIR had created **[107]** a Brahmachari Award.

It is thought that even now in 2021 some best medical research institutions of India or some first line medical colleges could be named after him to show gratitude to this human saint! The great man was born 19 December 1873 and he passed away on 6 February 1946.

At the present-day NRS Medical College, Kolkata the Department of Biotechnology of the Ministry of Science and Technology had approved in 2018, a project at NRS Medical College to work and provide comprehensive clinical care including diagnosis, management, multidisciplinary care, counseling, and prenatal testing of certain inherited medical disorders and that the institute would initially work on Thalassemia and congenital heart diseases. NRS Medical College, Kolkata is a renowned institute in India. The institute works and publishes scientific work, mostly related to the clinical and medical aspects of Cardiac Anaesthesiology, Cardiology, Cadiothoracic & Vascular Surgery, Dermatology, Endocrinology, Gynaecology & Obstetrics, Hematology, Medicines, Nephrology, Neurology, Ophthalmology, Orthopedics, Otolaryngology, Psychiatry, Radiotherapy, Respiratory Medicine, and Urology. They also publish in aspects of Pediatrics, Pediatric Surgery, Pharmacology, Physical Medicine and Rehabilitation, Anatomy, Biochemistry, Microbiology, Pathology, Community Medicine, Forensic Medicine & Toxicology and Plastic & Reconstructive Surgery. There is no division, however, which is involved in the synthesis of APIs and medical uses there of although the pioneering work of novel API development started in India from this institute.

Methaqualone

Methaqualone is chemically 2-methyl-3-(2-methylphenyl) quinazolin-4-one. Methaqualone was first synthesized and reported by Dr. Indra Kishore Kachar and Dr. Syed Hussain Zaheer in 1951 from Regional Research Laboratory, Hyderabad, which laboratory was renamed as Indian Institute of Chemical Technology. The inventors synthesised the molecule to assess its anti-malarial properties **[61]**. However, the inventors did not pursue further development on the molecule. Later on, a British Patent **[108]** was taken on the molecule by Toraude Lab. It is not evident from any published literature if the Indian laboratory challenged or protested to the grant of either the patent or whether the value of the molecule was further studied or pursued for its other properties. However, from the published literature it was clear that by 1965 in UK this molecule became a commonly prescribed sedative. The drug in combination with antihistamines became a popular sedative drug and was sold by the name Mandrex by Roussel Laboratories.In US, the drug was sold in the brand name Quaalude where it started to be manufactured as early as 1965 by Fort Washington, a Pennsylvania-based pharmaceutical farm **[109]** . Methaqualone is known by several other names. The molecule has the stoichiometric formula of $C_{16}H_{14}N_2O$, molecular mass of 250.3g/mole and has a serial number of 6028 on page 1019 in the Merck Index(Twelfth Edition) **[110]**. Presently, the use of methaqualone is banned in India and the substance is classified as a narcotic drug in the country **[62]**.

Enfenamic Acid

Enfenamic Acid also named as N-phenethylanthranilic acid having a molecular formula of C15H15NO2 and a molecular mass of 241.29 gm/mole is a non-steroidal anti-inflammatory analgesic substance. It has also anti-pyretic properties. The molecule was first synthesized by Hashim SR and Sattur PB .The inventors obtained two Indian patents namely Indian Patents No. 103066 and 114805, both in 1974. The patents were assigned to the Council of Scientific and Industrial Research (CSIR). Enfenamic acid has been enlisted at serial no. 3620 in the Merck Index **[111]**Twelfth Edition in 1996. The product has also been enlisted elsewhere **[112] .**

Both the scientists Hashim and Sattur were working at the Regional Research Laboratory, Hyderabad, which was a laboratory under the Council of Scientific and Industrial Research (CSIR). The laboratory was later renamed as Indian Institute of Chemical Technology from 1st April 1989.

After initial synthesis of the molecule by the Medicinal Chemistry Division of Regional Research Laboratory (RRL) Hyderabad of the CSIR in 1964 **[113],** followed by generation of pharmacological data, the clinical data generation required support which came from Unichem Laboratories Ltd. (Unichem), Mumbai. After several years of data generation and after having approval from the Drugs Controller General of India, Unichem commercialised **[114]** the product in 1981. Enfenamic acid was marketed by Unichem by the trade name Tromaril. Natriuretic properties of Tromaril were found to be interesting **[65]**. However, the drug is not in the market anymore. Several side effects of the drug have been reported earlier.

The two NCEs were discovered at the presently designated CSIR-Indian Institute of Chemical Technology (CSIR-IICT), Hyderabad. The institute was earlier known as the Regional Research Laboratory (RRL), Hyderabad. The history of the formation of the institute goes back to early 1940s. In order to facilitate industrial research in India, in the year 1940 the Imperial India constituted the Board of Scientific & Industrial Research (BSIR). Later, a BSIR was also established in Hyderabad in 1942, and two years later in 1944, the Central Laboratories for Scientific & Industrial Research (CLSIR)

was established. CLSIR was created to carry out similar functions in Hyderabad State. In the meantime, the Council of Scientific and Industrial Research (CSIR) was established at New Delhi and this body was registered as an autonomous body under the Societies Act in 1942. The then Government of India under the Imperial Government took advice from the the Royal Society, London. Professor AV Hill, Secretary of the Royal Society, London visited India in 1943 and identified Hyderabad as the location for establishing an Industrial research laboratory. Hyderabad was then the princely State of Hyderabad under the Nizam. After the independence of India from the British rule in 1947, the state of Hyderabad had merged with Independent India, and CLSIR started working closely with CSIR. Later, CLSIR was taken over by the CSIR on 13 April, 1956 and was renamed the Regional Research Laboratory, Hyderabad. The RRL, Hyderabad was retitled again as the Indian Institute of Chemical Technology (IICT) with effect from 1 April, 1989. It continues to function presently as the CSIR-IICT Institute. CSIR-IICT has the Department of Analytical and Structural Chemistry; Applied Biology; Catalysis and Fine Chemicals; Energy and Environmental Engineering division; Centre for Lipid Science and Technology; Centre for Natural Products & Traditional Knowledge; Fluoro-Agrochemicals division; Organic Synthesis and Process Chemistry division; Polymers & Functional Materials division; and Process Engineering and Technology Transfer division. The Institute has made outstanding contributions in various aspects of chemical and biological sciences in the country **[115].**

Hamycin

While working in Hindustan Antibiotics Limited (HAL), Pimpri, Pune, as the R&D Head, then designated as Superintendent R&D, Dr Mandayam Jeersannidhi Thirumalachar discovered the antibiotic Hamycin. He worked in HAL during 1956-75. He discovered during this period a number of antibiotics by the name Hamycin, Dermostatin, Aureofungin, MYc-4 and Tetraenenin. An US Patent was taken for a process for the production of Hamycin by HAL in 1966 where Dr. M.J. Thirumalachar was shown as the inventor **[11].**Hamycin was separated into Hamycin A and Hamycin B by countercurrent distribution and their properties were studied **[116]** . Hamycin A is the major component of the mixture.

Dr Thirumalachar was born on 22nd September 1914 in the erstwhile Mysore state of British India. His father was M.J. Narasimhan, who was a renowned mycologist and plant pathologist. Dr M.J. Thirumalachar graduated from Central College, Bangalore and obtained his Doctor of Science from the University of Mysore in 1944. He then moved to University of Wisconsin and secured a PhD under the supervision of Dr James G. Dickson **[117-118].** Dr Thirumalachar was a genius and his research areas and disciplines were very wide; he had interest in mycology, microbiology, antibiotics and chemotherapy **[119] .**

In 1967, for his contributions in Medical Sciences, the Council of Scientific and Industrial Research (CSIR) awarded him the Shanti Swarup Bhatnagar Prize **[120]** for Science and Technology, which is one of the highest Indian science awards.

After leaving HAL, Dr Thirumalachar worked as Professor in USA at the University of Minnesota Medical School. During this time, he was also serving for a while as the Visiting Scientist at the Danish Institute of Seed Pathology, Copenhagen. Thereafter, along with his son, he founded the Jeersaniddhi Anderson Institute, where he carried out advanced research in several aspects of plant pathology including mycology. He spent about two decades of his life in California at Walnut Creek, California where he died **[121]** at the age of 84 on April 21, 1999.

HAL was set up by the Indian government with the social objective of providing affordable drugs and was inaugurated by Jawaharlal Nehru,

India's first Prime Minister on 10 March 1954; the unit became operational in 1955. The UNICEF and the WHO had provided technological support on the production of bulk Penicillin G. Later, a state–of–the–art R&D unit was set up in the company with pilot plants to develop and improve processes based fermentation and down-stream processing for the manufacture of antibiotics. HAL maintained largest production of injectable penicillins and streptomycin in the country up to the late 1970s. It also created facilities for the manufacture of a wide range of formulations as tablets, capsules, injectables and large volume parenteral solutions.

HAL has to its credit several new discoveries including polyene antibiotics like Hamycin **[66]** (a pair polyene antimycotic organic compounds described as hamycin A and hamycin B) and aureofungin **[122-123]** (an antifungal agent). Aureofungin was indicated for use by HAL as a plant-antifungal protection agent.

Hamycin and Aureofungin were marketed by HAL as antifungal drug formulations in India and were used for treating fungal infections in human and plants respectively-Hamycin for human fungal disease and Aureofungin for plant fungal diseases.

Both Hamycin and Aureofungin are polyene antibiotics, produced by strains of streptomyces bacteria found in soil. Since these antibiotics were obtained from the soil of Pimpri, the microorganisms were named as Streptomyces pimprina. Hamycin is produced by the microbes in two forms, namely Hamycin-A and Hamycin –B as mentioned earlier. The antibiotics are close in chemical structural resemblance to Nystatin and Amphotericin B. When the author was working as a Manager in HAL during 1980-1982, the two drug substances were still manufactured and marketed. Presently, these drugs are not available in the market.

Hamycin had great possibilities of treating fungal infection; the drug formulation could be converted in to a less toxic formulation by liposomal methods. Some work in this direction had been done though liposomal formulations development of this drug but no new formulation was commercialized **[124-126].**

Later, HAL became a sick company and had to stop the production of all its bulk antibiotic production facilities .It remained sick for a couple of years. The company was reported to the Bureau of Industrial and Financial Restructuring (BIFR) in 1997. The company concentrated on production of selected formulations only. The performance later improved and on 17 January 2009 the company was taken off the books of the BIFR **[127-128] .** The company is operational and continues to manufacture and sell certain pharmaceutical formulations in the country.

Centimizone

While the scientists of CSIR-Central Drugs Research Institute (CSIR-CDRI), Lucknow were working for new antifilarial drugs, they synthesised an imidazole compound by the name 1-propan-2-ylimidazolidine-2-thione, later which was known as CENTIMIZONE, and which had the properties of binding to thyroid peroxidase, thereby preventing the oxidation of iodine/iodotyrosyl residues, which resulted in the inhibition of iodination of tyrosine residues in thyroglobulin and inhibition of coupling of iodotyrosine residues to form T3 and T4.From extensive studies, the compound CENTIMIZONE came out as a new drug to treat certain kinds of thyroid disorder. The initial observation of the increase in the weight of the thyroid gland of male albino rats was observed **[67]** and and the results were published in 1962.

The technology for the manufacture of the product and introduction of the pharmaceutical formulation of Centimizone in to the market was transferred to Unichem Labs Ltd, Mumbai and the product was approved for use by the Drugs Controller General of India in 1972. But the formulation was never introduced in the market **[129]**. The reasons for not introducing the formulation in to the market is not known.

Centbutindole

Centbutindole is an antipsychotic agent which was synthesized for the first time by the CSIR-CDRI in 1973 while the institute was working on the synthesis of butyrophenone derivatives. The international non-proprietary name of the compound is Biriperone. It is a dopamine antagonist; it also blocks 5HT2 receptors. In an intergroup comparative study of Centbutindole with Risperidone **[130]** (a well-known antipsychotic drug), the results showed that Centbutindole had similar clinical efficacy with Risperidone **[131]**. The properties **[132]** of the molecule can be seen at the cited reference. The IUPAC name of the compound is 1-(4-fluorophenyl)-4-(3,6,17-triazatetracyclo [8.7.0.03,8.011,16] heptadeca-1(10),11,13,15-tetraen-6-yl)butan-1-one.

The technology for the manufacture of the drug was transferred to Chemosyn Pvt. Ltd., Mumbai in 1987 but the product was never marketed by the company.

Ormeloxifene (Also known as Centchroman)

DL-Centchroman also known as Centchroman as well as Ormeloxifene is a non-steroidal selective estrogen receptor modulator. The drug was synthesised by a team of the Central Drug Research Institute, Lucknow and the process was protected **[71]** through an Indian patent in 1975**.** The Indian inventors were S. Ray, V. Kamboj, P. Grover, A. Kar and N. Anand.

The international non-proprietary name of the compound was later accepted as Ormeloxifene. Chemically, the compound is1-[2-[4-[(3S,4S)-7-methoxy-2,2-dimethyl-3-phenyl-chroman-4-yl] phenoxy]ethyl]pyrrolidine. This compound and others in a series was shown to be patented through US Patent No. 2822287 **[133]** dated 2 July, 1974 where the priority date for the invention was claimed to be 17 April, 1969. The inventor was J. Bolger and the patent was assigned to Rexall Drug Chemical, USA.

The Indian work was on finding and studying in depth the contraceptive activity of the compound. The substance was found to have contraceptive activity in rodents and primates. CSIR-CDRI then carried out further extensive research and developed the product as a non-steroidal, oral contraceptive for women, which is to be taken once-a-week. Later the compound was introduced for human contraception in July 1991 **[134]** . The substance is presently being manufactured and marketed as Saheli tablets by Hindustan Latex Limited, Thiruvananthapuram, India since 1992; the company changed its name **[135]** to HLL LifecareLtd. from 2009.Saheli tablets are oral contraceptives which are taken initially twice a week for the first three months and later once a week .

Centchroman is also converted into oral contraceptive tablets and sold by Torrent Pharmaceuticals Ltd., Ahmedabad as Centron tablets. Centchroman tablets are included in the Indian National Family Welfare Programme and are available as Chhaya tablets.

Centchroman tablets as oral contraceptives are available only in India. Besides use as contraceptive, Centchroman is also being experimented upon to find its efficacy to treat certain types of advanced breast cancer and dysfunctional uterine bleeding. Indian contribution to developing and marketing Centchroman tablets as oral contraceptives is a substantial contribution to contraceptive medicines.

In the CSIR-CDRI process of synthesis, the compound is synthesised by condensing 2,4-dihydroxy benzaldehyde with phenyl acetic acid in acetic anhydride-triethanolamine solution to get an intermediate chromene which is methylated at the hydroxyl moiety with methyl iodide in acetone and potassium carbonate slurry to give the methoxilatedchromene intermediate, which in turn is dimethylated with Grignard reagent comprising methylmagnesium iodide in tetrahydrofuran to produce 7-Methoxy-2,2-dimethyl-30phenyl-2H-chromene.

This intermediate on condensation with N-(Pyrrolidino) ethoxy benzene hydrochloride by Friedel-Craft reaction using anhydrous aluminium chloride in ethylene dichloride as solvent gives Centchroman hydrochloride. The overall yield is low though the material has the desired purity **[136]**. Centchroman is considered to be an outstanding product of research from India.

Centpropazine

Centpropazine is an antidepressant drug which was discovered at CSIR-CDRI in 1972. The IUPAC name of the chemical is 1-[4-[2-hydroxy-3-(4-phenylpiperazin-1-yl)propoxy]phenyl] propan-1-one.

Depression is a cause of great burden in providing effective health services to people. Depression in extreme conditions can hasten suicides. Depressions must be treated and several effective options are available. Multi-centric trials carried out in patients of depression with Centpropazine had shown **[137]** that the drug had wider safety margin in acute toxicity studies when compared with the standard drug Imipramine. The results established a safer profile of the drug on a patient population of 42 only and, therefore, needed further elaborate studies. The results of antidepressant response were useful for further evaluation. The technology for the manufacture of the drug was transferred by CSIR-CDRI to Merind Ltd., Mumbai in 1996 but the drug was not marketed by the company; the reasons for not marketing are not known. In a review paper written later in 2010, the CSIR-CDRI scientists had compared the efficacy of a large number of antidepressants; the efficacy of Centpropazine was reported to be similar **[138]** to Imipramine.

Centbucridine

Centbucridine **[139]**is a local anesthetic. It is a quinolone derivative. The chemical name of the product is 4N-Butylamino-1, 2, 3, 4-tetrahydroacridine. The compound is usually presented as the monohydrochnoride derivative.

Preoperative and perioperative conditions of a surgical operation often require use of local anesthetics. There has been a pressing need in the country to have an efficacious, safer, low dose local anesthetic drug. Such a drug should have fast onset of action and the duration of anesthetic action should be short or not very long. To meet such requirements, the CSIR-CDRI scientists synthesised several compounds, among which came out Centbucridine. Generally the industrially used local anesthetic drugs are chemically either **[140]** aminoesters or aminoamides. Commonly used **[141]** local anesthetic aminoesters are cocaine, benzocaine, procaine, etc. and the aminoamides are lidocaine, bupivacaine, prilocaine, etc. Centbucridine does not have any structural similarity with these compounds and is chemically a quinolone derivative. The efficacy profiles of Centbucridine was evaluated in comparison with lidocaine **[142-144]** and Centbucridine was found to be comparable with lidocaine in terms of efficacy and safety characteristics. It had been claimed **[145]** by CSRI-CDRI that from many aspects Centbucridine was superior to lignocaine.

CSRI-CDRI mentioned that the technology for the manufacture of Centbucridine had been licensed to Themis Chemicals Ltd., Mumbai in 1987. The company was to market the product under the brand name 'Centoblok'. However, the product could not be found in the market. Published information indicated that the product was not marketed by the company **[146]** even though the technology was procured by them.

Alpha, beta-Arteether

CSIR-CDRI was working in collaboration with Central Institute of Medicinal and Aromatic plants (CIMAP), Lucknow on the plant *Artemisia annua* to develop antimalarial drugs from the plant metabolites and in the process came up with Alpha, beta-Arteether which is a semi-synthetic derivative of artemisinine. Artemisinine is an active metabolite present in the plant. Artemisinin is not well absorbed by

the human gastrointestinal tract and therefore its availability in to the blood in therapeutic quantities is a problem which was to be solved. The scientists of CDRI therefore prepared several derivatives of this product in order to increase the bioavailability. In such an endeavor of investigation; they came out with arteether which is the ethyl ether of dihydroartemisinin. This compound was prepared by a two-steps process wherein the first step, artemisinin was reduced to dihydroartimisinin using sodium borohydride and in the second step the dihydroartimisinin was converted in to arteether by an acid catalyzed reaction. The converted product was a mixture of alpha-arteether and beta-arteether in proportions of 30 to 70; the alpha-arteether was an oily material while the β-arteether was crystalline.

Each of these isomers had shown antimalarial properties and CDRI decided to use the mixture as an antimalarial drug and started clinical evaluation of the mixture to treat P. falciparum malaria. The formulations prepared from Arteether were subjected to extensive clinical trials at seven malaria prone areas of India and provide evidence of excellent efficacy response to treat P. falciparum malaria **[147-148]** .Based on the results of efficacy and safety of thee formulations of Arteether invented by CDRI, the Indian Drugs Controller had permitted its use to treat P. falciparum malaria in hospitals and nursing homes. CDRI had licensed **[149]** Themis Medicare Ltd., Mumbai in 1997 to manufacture and sell the Arteether formulation.

The active ingredients of the injectable formulation are a mixture of alpha and beta isomers of arteether in proportions of 30:70 and are formulated to contain 150 mg/ml of the active ingredients. The product is introduced in the market in the trade name of E-Mal as an injectable formulation.Injections of Arteether are to be used as a second line of treatment in severe P. falciparum malaria of chloroquine resistant cases and in cerebral malaria in order to prevent the emergence of resistant cases of the disease. Several independent studies in India have proven the efficacy of the Arteether formulation to treat P. falciparum malaria **[150-151]**.

The discovery of antimalarial drugs from Artemisinin, a sesquiterpene lactone containing a unique peroxide bridge, and isolated from the solvent-extracted material of the plant Artemisia annua emanates from the extensive Chinese research **[152]**,started in late 1960s to find an effective drug to contain malaria. Artemisia annua is an herb which is employed in Chinese traditional medicine as a folk medicine to treat malaria. The pioneering Chinese investigation had eventually ushered a new era for the treatment of malaria. The whole hearted investigation carried out by a large number of people of different skills covering the fields of chemistry, medicinal chemistry, pharmacognosy, pharmacology, toxicology, pharmaceutics, clinical investigators as well as the industry made the break through possible.

Malaria is caused by a single-cell parasite that causes severe fever. The lead Chinese scientist YouyouTu while working on the traditional Chinese medicine sweet wormwood (Artemisia annua) to treat malaria fever was able to extract the active ingredient, artemisinin, which was found to inhibit the growth of malaria parasite. Based on this lead on artemisinin further work was vigorously initiated which led to the discovery of several antimalarial drugs that were responsible for the survival of millions of people all over the world suffering from malaria. Madam YouyouTu obtained Noble Prize for her work. The Indian work is considered to be an extension of the Chinese work on Artemisia annua and the development of Alpha-beta-Arteether technology. Indian work could be pursued based on the then contemporarily published research work where intellectual property rights (IPR) were not as stringent as it were later after countries became Members of the World Trade Organization (WTO), to which India became a party and had to modify its IPR consistent with the provisions of the trade related intellectual property rights (TRIPS) of WTO and consequently, the new Indian Patents Act

was enacted with effect from 01.01.2005. The earlier Indian Patents Act 1970 enabled India to carry out developmental activities on any chemical even if patented, by using inventive non-patented processes. This law assisted India tremendously to develop inventive processes of already IPR protected molecules (elsewhere as also in India). Technology development for Arteeher (Alpha, beta-Arteether) is one example of India's gaining from the then Patents Act. This technology of Arteether on use saved the lives of a large number of malaria infected people, especially the chloroquine resistant P. falciparum malaria infected patients. Alpha/beta-Arteether is described chemically **[153]** as a product of empirical molecular formula C34H56O10 with molecular weight of 624.8 g/mol.

Bulaquine (Elubaquine)

The CSIR-CDRI had developed **[82,83,154]** an antimalarial Drug, to which initially the identifying house number was "Compound 80/53".Its International Nonproprietary Name (INN) is Bulaquine which is also known by another name of Elubaquine. The IUPAC name **[155]** is (3E)-3-[1-[4-[(6-methoxyquinolin-8-yl) amino] pentylamino] ethylidene] oxolan-2-one. CDRI was involved in the search for analogues of Primaquine and came up with Bulaquine. Bulaquine is an 8-aminoquinoline derivative like Primaquine. Bulaquine is distinguished and differentiated from Primaquine by having one H replaced at N1position by 3-ethylidinotetrahydrofuran-2-one of the 1, 4-pentanediamine compound Primaquine. Bulaquine is considered to be a prodrug of Primaquine.

Bulaquine was clinically evaluated on human subjects against P. vivax in Thailand **[156]** and was assessed to be commensurable to Primaquine in terms of safety and tolerability. In clearing gametocytemias of P. falciparum in patients with acute infections,Bulaquine was assessed to be superior **[157]** to Primaquine. Malaria eradication efforts are extremely important areas of social welfare especially in the tropical countries and in this context the prospects of Bulaquine and other aminoquinoline derivatives have been extensively reviewed **[158-159]** .Bulaquine is synthesized **[160]** by condensation of Primaquine with acetyl butyrolactone using piperidine as the condensation base. CSIR-CDRI had transferred the technology of Bulaquine to Nicholas Primal India Ltd, Mumbai in 1999 for marketing the product. The company has introduced Bulaquin as a combination with Chloroquine under the trade name Aablaquine **[161].**

The CSIR-CDRI, Lucknow is a premier drug research institute of India. The institute was inaugurated by the then Prime Minister of India Pt. Jawaharlal Nehru on 17 February, 1951 with a vision to strengthen and advance the field of drug research and development in the country. Over the past 70 years, the institute has been contributing to chemical and biomedical research driven new drug discovery and development besides making great advancement in the understanding of disease biology in the areas of national priorities. The areas of research of the institute include malaria and other parasitic diseases; antimicrobial resistance; viral diseases; cancer biology area; neuroscience & ageing biology; cardiovascular system disorders; bone health and metabolic bone diseases; reproductive health research; and multiple pre-clinical studies. The institute has glorious achievements in multiple areas, which include discovery of new drugs; development and transfer of several technologies to the industries; development of diagnostics based on PCR techniques, Direct Agglutination tests ,LDH-based diagnosis of malaria among others; and generation of multiple patents **[6]** .

Chandocuronium iodide

Chandocuronium iodide is a skeletal muscle relaxant which falls in the category of non-depolarizing neuromuscular-blocking agents

or drugs. The chemical was synthesised while the investigators under the leadership of Prof. Harkishan Singh of Punjab University, Chandigarh, India were working in search of newer drugs for the replacement of succinylcholine chloride. The whole area of neuromuscular blockers that have been isolated or synthesized and assessed for their usefulness during surgery with anaesthesia to cause the relaxation of muscles and control of their movement has been extensively reviewed and chandonium iodide was found to secure an important place among the aminosteroids (azasteroids) synthesized and evaluated **[84,162-164].**

Chandonium iodide **[165]** is presently named as Candocuronium iodide .Earlier the substance was identified as HS-310, which was the name given by the inventors**.** The compound is chemically named as (4aS,4bR,8S,10aR,10bS,12aS)-1,1,10a,12a-tetramethyl-8-(1-methylpyrrolidin-1-ium-1-yl)-3,4,4a,4b,5,7,8,9,10,10b,11,12-dodecahydro-2H-naphtho[2,1-f]quinolin-1-ium dioxide. Chandonium iodide is also referred to as 17a-methyl-3beta-pyrrolidino-17a-aza-D-homo-5-androstene dimethyl iodide.

The technology for the synthesis and manufacture of Chandonium iodide from the basic stage was developed jointly by the scientists of Punjab University and CDRI, Lucknow. The synthesis part was developed at Punjab university while the biological part including information generation on clinical research at CDRI. The technology package was then transferred by the CDRI to Ranbaxy Labs Ltd., New Delhi in 1987 and to Cipla Ltd., Mumbai in 1995.The formulations of Chandonium iodide are not available in the market however, the reasons for which are not known.

Prof Harkishan Singh **[166]** (25 November 1928–20 March 2020) was working at the Pharmaceutical Chemistry Division of Punjab University where the research work on Candocuronium iodide was carried out. He joined Punjab University as a Reader in 1964 and later became the Professor and subsequently the Dean, Faculty of Pharmaceutical Sciences. During his later days from 2003, he was the Professor Emeritus.

The University of Punjab was established initially at Lahore (now in Pakistan) in 1882. Preceding the establishment of this University were established three other major Indian Universities namely the University of Calcutta (set up on January 24, 1857), the University of Bombay (July 24, 1857) and the University of Madras (September 5, 1857). All these Universities and newer others established later have made India rich in education and culture. The University of Punjab, popularly known as Punjab University **[167]** (also spelt a Panjab University) has the distinction of inventing a new chemical entity which became a novel API and was in the market for a while as discussed here in under. But before that, more is described on the University of Punjab. After the partition in 1947, the Indian part of Punjab – East Punjab and the Indian part of the Punjab University, then known as the East Punjab University went through traumatic changes. After partition, in 1950 two separate states were created, namely the Punjab state which included the former Raj province of Punjab, and the other comprising the princely states of Patiala, Nabha, Jind, Kapurthala, Malerkotla, Faridkot and Kalsia and known as the Patiala and East Punjab States Union (PEPSU). The PEPSU was merged into the Punjab state in 1956, and the present Punjab state was created **[168]** . After Chandigarh was selected as the capital of the Punjab state, a red sandstone campus was designed for the Panjab University by Pierre Jeanneret under the general guidance of Le Corbusier. The Panjab University moved at the new campus gradually during 1958-1960.

Punjab University pursues excellence in teaching and research in science and technology, humanities, social sciences, performing arts and sports. The University is located in Sector 14 and Sector 25 of Chandigarh; spread over an area of about 550 acres. The University has a

Dean for Research who functions and operates under the patronage of the Vice Chancellor. Dean for Research promotes high quality research activities in the University and coordinates with various national and international academic and funding bodies. The Department of Chemistry of the University was founded by Dr. S. S. Bhatnagar at Lahore in 1925; this department at the present campus at Chandigarh is one of the prestigious departments of Panjab University. The Department has on its faculty highly competent and efficient members whose work is internationally recognized.

Nitroxazepine (Sintamil)

Nitroxazepine, chemically known as 10-[3-(dimethylamino) propyl]-2-nitrodibenzo [b, f][1,4] oxazepin-11(10H)-one was synthesized **[86]** for the first time by Hindustan Ciba-Geigy in its R&D establishment in India by K. Nagarajan and V. P. Arya and the drug was introduced for sale by the company in 1982. Hindustan Ciba-Geigy was later on taken over by Novartis. Novartis continues to sell the product in the brand name Sintamil. The drug is an antidepressant and is used for the treatment of depression.

Nithicocyamine (Amoscanate)

Nithiocyamine, which is also known as AMOSCANATE, is a broad spectrum anthelmintic drug. The active pharmaceutical ingredient belongs to the class of arylisothiocyanates. The drug is active against a wide range of nematodes such as roundworm, hook worm and filarial; cestodes such as the tape worms, and trematodes such as the schistosomes. The product was synthesized **[86]** for the first time in the CIBA-GEIGY Research Centre, Mumbai. The IUPAC name of the compound is 4-isothiocyanato-N-(4-nitrophenyl) aniline. The properties of amascone are described elsewhere **[169]** . The formulations of amoscanate, presented in the form of tablets were approved **[170]** for use in India in November, 1985 for treating adult hookworm infestation.

Saroglitazar

Cadila Healthcare Limited (CHL), Ahmedabad, Gujarat was engaged in the synthesis of novel antidiabetic drugs and produced a large number of novel heterocyclic compounds which included synthesis **[171-172]**of innovative beta-aryl alpha substituted propanoic acids and their derivatives. Two new antidiabetic drugs **[173-174]** came out from these investigations one of which was a compound of molecular formula of C25H29NO4S and molecular mass of 439.57 g/mole and the other was the magnesium salt of the above compound of molecular formula is [C25H28NO4S]2 Mg and the molecular mass900 g/mole.

The company introduced **[175]** the drug Lipaglyn (saroglitazar) in June 2013. Lipaglyn was found **[176-177]** to act as dual regulator of lipids and glucose metabolism by activating peroxisome proliferator-activated receptors (PPAR). The molecule is claimed to possess two main classes of PPAR agonists namely the PPARα (alpha) and PPARγ (gamma). It manifests both lipid and glucose-lowering effects. It lowers the high blood triglycerides as well as blood glucose. Further, it improves the insulin resistance. The marketed formulation is available in the form of tablets of 4mg dose for oral administration.

CHL is a research-based pharmaceutical company. The company was incorporated in May 1995 and it became a public limited company in July 1996.CHL belongs to the Zydus Cadila Group, Ahmedabad, India. The product range of the Group includes a wide range of active pharmaceutical ingredients and formulations thereof. The Group also produces a sizable number of modern biotech products including vaccines.

Diperoxochloric Acid

Diperoxochloric Acid, was co-developed through a collaboration between Centaur, Mumbai and Cyto Tools **[178]**AG, Germany. Centaur Pharmaceuticals Private **[179]** 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 to be tested for the treatment of diabetic foot ulcer. The molecular formula **[180]** of Diperoxochloric acid is Cl2O6 and the molecular weight is 166.9 g/mol. Diperoxochloric acid 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 **[181]** on the formulation derived from Diperoxochloric acid. Based on the results of Phase-III trials, the drug was approved for human use in India by the DCGI in 2020. The novel formulation of Diperoxochloric acid was launched by Centaur **[182]** in October 2020 by the trade name 'WOXheal' and was indicated for the in the treatment of Diabetic Foot Ulcer.

For a country of Indian magnitude, the 16 numbers of novel APIs discovered over the years is considered very small. Does this imply that there was not much enabling multidisciplinary infrastructure, funding support, enabling regulatory bodies, political will and societal encouragement for cracking a disease problem? Did the government invest enough for this? Was there adequate policy support for the entrepreneurs to invest on the development of novel APIs? Did the private sector invest enough money in their R&D infrastructure for developing novel NCEs? Moreover, it also needed to be ascertained if the inventors could adequately reap the benefits of their discovery in terms of societal recognition or amassing wealth? Could the Indian environment attract the best talents to devote their career in the discovery of novel APIs in India or there were more attractive other easier opportunities for accruing more wealth? These are some of the questions around which answers were being looked for in the next chapter.

IV

India's Efforts on Novel APIs by Various Actors after 1947

In Table 1 the novel APIs emanating from India have been described. The three sectors of the business entities namely the Indian public-funded institutions, the foreign multinational companies and the Indian private sector companies have contributed to such endeavor and efforts. There is a need to discuss more on what efforts have also been made towards novel API development.

The Public-Funded Institutions

As has been mentioned, the Regional Research Laboratory, Hyderabad (later renamed as Indian Institute of Chemical Technology (IICT), Hyderabad); All India Institute of Medical Science(AIIMS), New Delhi; Hindustan Antibiotics Ltd, Pimpri, Pune, Maharashtra; Central Drugs Research Institute, Lucknow; and Punjab University, Punjab had made visible contributions towards such efforts. Several other public-funded institutions had also made considerable efforts. These include the CSIR-Institute of Microbial Technology (CSIR-IMTECH), Chandigarh; the Regional Research Laboratory, Jammu (renamed as Indian Institute of Integrative Medicine [CSIR-IIIM], in 2007); Indian Institute of Chemical Biology,(CSIR-IICB) Kolkata; CSIR-Institute of Genomic and Integrative Biology (CSIR-IGIB), Delhi; CSIR-Central Institute of Medicinal and Aromatic Plants (CSIR-CIMAP), Lucknow; CSIR-Centre for Cellular and Molecular Biology(CSIR-CCMB), Hyderabad; CSIR-National Chemical Laboratory(CSIR-NCL), Pune; CSIR-Institute of Himalayan Bioresources Technology (CSIR-IHBT), Palampur; CSIR-Industrial Toxicological Research Centre(CSIR-ITRC), Lucknow; CSIR-National Botanical Research Institute (CSIR-NBRI), Lucknow; and CSIR-Central Salt &Marine Chemicals Research Institute (CSIR-CSMCRI),Bhabnagar.

The CSIR-Institute of Microbial Technology (CSIR-IMTECH), Chandigarh, was established in 1984.The institute specializes in molecular and cell biology, immunology, structural biology, microbial genetics including yeast genetics , microbial taxonomy; proteomics and protein engineering, fermentation technology and bioinformatics. CSIR-IMTECH has developed profound expertise in cloning and expression of recombinant/engineered proteins and their scale-up; protein structure determination through X-ray crystallography; screening of microorganisms for novel enzymatic activities and strain improvement; among others. IMTECH is also the site for the microbial culture type depository. CSIR-IMTECH was set up to be a fore-runner in the niche domain of microbial biotechnology **[183-184].** CSIR-IMTECH is involved in the discovery of novel technologies for drugs; they have developed technologies for the manufacture of streptokinase, a thrombolytic protein drug in various forms namely the natural one as also the r DNA based streptokinase and

its pegylated form **[185-186].** These technologies have been transferred to industry. No novel API has however been developed by the institute yet.

Indian Institute of Integrative Medicine of CSIR (CSIR-IIIM), Jammu is engaged with primary focus of research on drug discovery from natural products **[187].** Natural product sources include medicinal plants and microbial species. They also specialise in fermentation techniques. They have developed certain drug technologies such as production of metal-gluconates by fermentation, enrichment of natural calcitriol, hepatoprotective herbal formulations etc. No novel API has yet been produced.

The present CSIR-Indian Institute of Chemical Biology(CSIR-IICB) is an off- shoot of the research extension of Indian Institute for Medical Research(IIMR), an establishment which was created in 1935 in Calcutta for biomedical research. The name of IIMR was later changed to the Indian Institute of Biochemistry and Experimental Medicine. Calcutta. In the year of 1956, the institute was included within the aegis of CSIR. The institute was again renamed to the present one in 1982. CSIR-IICB specialises in medicinal chemistry, chemical synthesis, extraction of natural products, phytochemicals, study of infectious diseases especially leishmaniasis and cholera, immunology, metabolic disorders/ diseases, molecular biology, cell signalling and cellular biology, pharmacology, genomics, proteomics . structural biology and bioinformatics **[188]**. The institute claims to have developed certain drug formulations based on plant extracts which are marketed **[189]** as ASMON, a herbal medicine for the treatment of Asthma, and PROSTALYN, a herbal extract for the treatment of benign Prostate hyperplasia. PROSTALYN preparation is based **[190]** on use of *Murraya koeniggi* and *Tribulus terrestris*. However, the active ingredients have not yet been chemically characterized. No novel API has yet been developed by the institute.

In all the other CSIR institutes, besides multiple types of investigation involving cellular and molecular biology, work is also being carried out to discover novel active pharmaceutical ingredients, besides other scientific work. While all these institutes have immensely contributed to newer and novel understanding in various facets of cellular and molecular biology of different life forms, none have yet come out with any defined novel API.

Foreign Multinational Companies

In the private sector, the work done by the branches and the sister concerns of the multinational foreign companies (MNCs) such as those carried out at Ciba-Geigy Research Centre, Bombay (later renamed as Hindustan Ciba-Geigy) was most significant. As mentioned in Table 1, two synthetic drugs by the names Nitroxazepine (an antidepressant) and Amoscanate (a broad spectrum anthelmintic drug) came out from their research. The company decided to discontinue **[191]** further basic research using the skills of synthesis at their Goregaon research facilities because of inadequate return from the efforts. In the meantime worldwide the emphasis in pharma research shifted from chemotherapeutic research to development of products by using techniques of modern biotechnology. The Goregaon Research Centre of the company continued for over 25 years but no promising new compounds were in the pipeline. The decision of Hindustan Ciba Geigy to close down the chemotherapeutic research centre based of chemical synthesis was a great loss to India.

Several other 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 were significant. However, no new drugs came out from their research efforts that got the regulatory approval for use in human subjects. Most of these multinational companies have later on either

merged with other multinational companies or have been acquired by others. Hoechst Research Centre, Bombay which was owned by the Hoechst was started in 1972. While searching for the history, it was revealed **[192-193]** that a company by the name Hoechst Fedco Pharmaceutical Private Limited was incorporated in India in 1956. The name of this company was changed to Hoechst Pharmaceuticals Private Limited in 1959; later, the name was changed to Hoechst India Limited in 1984 and even later in 1996 to Hoechst Marion Roussel Limited. In 2001, Aventis Pharma Limited became the Group's listed entity in India and in May 2012 Aventis Pharma became Sanofi India. Hoechst Research Centre is no more with Sanofi India; it was acquired by Piramal Enterprises Ltd., Mumbai in 1998. Sanofi India is owned jointly by Sanofi, France and its 100 per cent subsidiary - Hoechst GmbH, Germany who together hold majority shares (60.4 per cent of its paid-up share capital) in 2020.

Smith Kline & French **[194]**, Bangalore was earlier owned by Smith Kline & French Laboratories, an American company. SmithKline & French merged with Beckman Inc in 1982. The name was thereafter changed to SmithKline Beckman. In 1989, this company merged with Beecham to form SmithKline Beecham P LC and the headquarters were moved from the United States to England. In December 2000, Glaxo Wellcome and SmithKline Beecham merged forming Glaxo Smith Kline (GSK). The company's global headquarters were officially opened in 2002 at GSK House, Brentford, London. The R&D outfit of Smith Kline & French, Bangalore was closed down.

Astra Research Center, Bangalore was established **[195]** in 1985 and was later named the AstraZeneca R&D Center, following the merger of Astra and Zeneca. Initially the research center was started inside the Indian Institute of Science (IISc), Bangalore campus and later it was moved out to Aranya Bhavan in Malleswaram, Bangalore. The establishment was conducting research on neglected tropical diseases, diarrheal diseases, malaria, and tuberculosis. In January 2014, the management decided to close down **[196]** 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 on basic and application-oriented research for drug discovery in India in spite of the fact that India had a sizable number of trained man-power and that the developmental infrastructure in the country was comparatively cheaper.

Indian Private Companies

The history of the Indian pharmaceutical industry **[197]** dates back to 1901 when Bengal Chemical and Pharmaceutical Works Pvt. Ltd, Kolkata, was started. There is mention of at least of two other Indian companies, which made significant contribution in the production of allopathic medicines, founded earlier than 1901 - B. K. Paul & Co, Kolkata, and N. Powell & Co, Mumbai, which pioneered essentially in the imports and distribution of allopathic medicines along with production of certain other local medicines. Setting up of Bengal Chemical was followed by the establishment of Alembic Pharmaceutical Works, Baroda in 1907, Zandu Pharmaceutical Works Ltd, Kolkata in 1910, Calcutta Chemical Company, Kolkata, in 1916, and Bengal Immunity, Kolkata, in 1919. These companies had started essentially with the zeal of patriotism to compete with the imported medicines of British companies and foreign MNCs. Indian companies were not yet technologically rich and could not freely produce and supply "patented medicines" to the people of India because of multiple barriers, the legal barriers being of prime significance. But Indian entrepreneurs continued to show their enthusiasm to capture a part of the business, which grew steadily. During 1930s and 1940s, several other Indian companies came up. Noteworthy among them were Cipla,

Mumbai (established in 1935); Amrutanjan Health Care, Chennai (registered in 1935); East India Pharmaceuticals Ltd, Kolkata (formed in 1936); FDC Ltd, Mumbai (established in 1940) ; Dey's Medical Stores, Kolkata (started as a retail medical store in1941 followed by factory in 1957); Indoco Remedies, Mumbai (incorporated in 1947); and IPCA Labs, Mumbai (established in 1949).

Based on the scattered information left by these companies in their history-sheets as obtained from the sites of the companies on the net, it was observed that Indian entrepreneurs initially produced pharmaceuticals dispensed in various formulated forms such as tablets, dry powders, capsules, liquids, ointments and other forms, dispensed as alkalizers, digestives, immune boosters based on traditional herbal medicines, disinfectants(based on coal- tar products), plant-based astringents, balms for pain relief and alcoholic herbal extracts of different kinds.

Development of APIs was far from imagination in Indian companies due to various reasons which were deficiencies in economic conditions, technological insufficiency and inadequacy of skills in synthesis, infrastructural limitations and other reasons such as IPR issues. New chemical entities (NCEs) and APIs were scarcely available. Whenever APIs were available in the country, these were sourced mostly from the multinational companies. Several modern APIs used to be the patent-protected proprietary products of the multinational companies, and, therefore, use of such bulk drugs for turning out formulations and using foreign brand names for respective formulations by the Indian collaborators required payment of heavy royalties to foreign companies, which were often not affordable. Yet, a few Indian companies ventured to manufacture patent-expired APIs from the basic stage. Such efforts were made mostly after the independence; though a few were manufactured earlier also from the available raw materials. Production of APIs in India in significant way started after independence, first in the public sector companies and later in private Indian companies.

Among the Indian private companies, significant R&D work for new products and new process developments on APIs were carried out in later periods of 1960s and thereafter. Such efforts intensified only after the Indian Patents Act 1970 was promulgated. Significant R&D expenditure was made at several Indian companies during 1970s and thereafter. Such efforts culminated into the establishment of a sound Indian pharmaceutical industry comprising setting up of manufacturing units for a wide range of generic APIs and formulations thereof.

It is necessary in this context to take a stock of the expertise developed within the country in handling multiple complex chemical and biochemical reactions in industrial scale and the number of generic APIs being manufactured including especially those which are being profoundly exported. Assessments of these capabilities are indicators of expertise among others, towards technical preparedness for working for developing capacities for inventing novel APIs.

Although India has invented only a few novel APIs in the Indian private sector industries thus far, efforts can be made to ascertain and assess what further steps can be taken individually as well as collectively to strengthen the country to move towards faster development of novel APIs during the future years. According to the study, of the total number of generic API manufacturing companies in India which are presently in operation, the more significant ones in the Indian private sector in terms of value creation are not more than 1000 by the end of 2020. The study had chosen and has a list of 60 companies which are operating in the Indian private sector, and have or had made significant contributions in the manufacture and supply of generic APIs to meet the internal demand as well as exporting their generic APIs with adequate value creation. This information is important in the context of learning what generic APIs are being exported with value creation in the present situation of intense market competition and maintenance of high quality and efficacy standards in a domain

and surrounding of pressure from the society and the government for the maintenance of acceptable standards of discharge of solid, liquid and gaseous discharges from factories. This also provides insight into the areas of high expertise developed by the industry in chemical synthesis, unit operations and unit processes where India has acquired skills of high standards. The list of the chosen sixty companies is as under:

Alchem International, New Delhi; Alchem laboratories, Mumbai; Aarti Drugs Ltd, Palghar, Maharashtra; Alembic Pharmaceuticals Ltd, Vadodra; Allastir Pvt Ltd, Chennai; AnjanDrug Pvt Ltd, Chennai; Aurobindo Pharma, Hyderabad; Basic Pharma, Ankleshwar, Bharuch; Biocon Ltd, Bangalore; Cadila Laboratories, Ahmedabad; Centaur Pharmaceuticals Pvt Ltd, Mumbai; Century Pharmaceuticals, Mumbai; Cipla, Mumbai; Concord Biotech Ltd, Ahmedabad; CTX Lifescience Pvt Ltd, Sachin, Surat; Dabur Research Foundation and Dabur Pharma Limited, Gaziabad, UP; Dr. Reddy's Laboratories, Hyderabad; Divi's Laboratories, Hyderabad; Elder Pharma, Mumbai; Elixir Pharma , Ahmedabad; Emcure, Mumbai; FDC Ltd, Mumbai; Glenmark Pharmaceuticals Ltd, Mumbai; Granules India Limited, Madhapur, Hyderabad; Halcyon Labs Pvt. Ltd, Ahmedabad; Hetero Drugs, Hyderabad ; IOL Chemicals and Pharmaceuticals Limited, Ludhiana; IPCA Labs, Mumbai; J B Chemicals & Pharmaceuticals Ltd, Mumbai; Jubilanr Pharma, Noida, UP; Kothari Phytochemical International, Kolkata; Lupin Ltd, Mumbai; Mankind Pharma, New Delhi; Marksans Pharma Ltd, Goa; Matrix Pharmaceuticals, Hyderabad; Meck Pharmaceuticals and Chemicals Pvt. Ltd, Ahmedabad; Medilex Laboratories, Pithampur, MP; Natco Pharma, Hyderabad; Nicholas-Piramal, Mumbai; Orchid Pharma, Chennai; Palam Pharma Pvt. Ltd., Ahmedabad; Panacea Biotech, Delhi; Pro Vinus Life Sciences, Chennai; Ranbaxy laboratories, New Delhi and its Ranbaxy Research Foundation; Reliance Life Sciences, Mumbai; Sarabhai Chemicals, Vadodra and its associates; Shilpa Medicare Ltd, Hyderabad; Solara Active Pharma Sciences, Chennai; Sun Pharmaceuticals, Mumbai; Suven Pharmaceuticals, Hyderabad; Symbiotec Pharmalab Limited, Indore; Syngene International Pvt Ltd, Bangalore; Torrent Pharma, Ahmedabad; USV Ltd, Mumba; Unichem Labs Ltd., Mumbai; Varahi International, Ahmedabad; Vasuda Pharma, Telengana; Wockhardt Ltd, Mumbai; ZCL Chemicals, Mumbai; and Zydus Cadila, Ahmedabad.

A brief write-up on each of these companies has been provided below, in order to have a flavour and acquaintance with these sample companies on their skills, aims and objectives as also their interest and investments made towards the development of novel APIs.

Alchem International Pvt. Ltd, New Delhi

Alchem International **[198-199]** Pvt. Ltd, headquartered at New Delhi and having the manufacturing factory at three locations in India is a company packed with activities in medicinal plants and phytochemicals, which are used in therapy, as nutraceuticals and in cosmetics industry. It products are in a wide range of therapeutic categories, which include remedies for cough and cold; joint stiffness and joint pain; liver disorders; constipation; prostate problems; indigestion; acidity and different kinds of common gastrointestinal disorders. The company was founded in 1935. The company is essentially an export orientated one with sales in over 35 countries. Alchem International manufactures and supplies **[200]** nearly thirty numbers of generic APIs, which are either derived from plant-sources or are products which are semi-synthetically modified phyto-chemicals. Alchem International is not involved in the development of novel APIs.

Alkem Laboratories Ltd, Mumbai

Alkem Laboratories Ltd, **[201-204]** presently headquartered in Mumbai was incorporated on 8 August 1973 at Patna as Alkem Laboratories Private Limited. Subsequently on and from 26

October 1988, the name was changed to Alkem Laboratories Limited. The company was started by Samprada Singh, who became a billionaire and one among the richest persons in the world. Alkem Laboratories is a multinational Indian company engaged in the development, manufacture and sale of pharmaceutical formulations, nutraceuticals and certain generic APIs. The manufacturing facilities were established at Taloja, Maharashtra and thereafter the company made much progress. The company has put more emphasis on the manufacture and sale of branded generic formulations, and has a portfolio of more than 700 brands, which are sold in India. Over the years, the company had acquired a large number of pharmaceutical companies such as Pharmacor Pty Ltd, a generic pharma company in Australia; Ascend Laboratories, a generic marketing company in the US; and Enzene Biosciences Ltd , Mumbai, a company engaged in the development of similar biologics in India. The R&D of the company is mainly on the development of generic and branded pharmaceutical formulations. It also develop novel processes for the manufacture of generic APIs and drug-intermediates. The company has not invested on the development of novel APIs. Certain novel processes developed by the company have been patented **[205]**.

Aarti Drugs Ltd, Palghar, Maharashtra

Aarti Drugs Ltd **[206-207]**, Palghar, Maharashtra was established in the year 1984. The company is a part of $900 Million Aarti Group of Industries. It established its R&D Division at Tarapur, Maharashtra Industrial Development Corporation (MIDC). Their manufacturing facilities are located at Tarapur (Maharashtra) and Sarigam (Gujarat). The company has claimed to be capable of manufacturing over 50 bulk chemical entities including generic APIs and multiple numbers of intermediates and speciality chemicals. At present they are manufacturing and exporting 28 numbers of generic APIs in several therapeutic categories such as anti-inflammatory drugs, cardioprotectants, anti-diarrhoeal drugs, antifungal drugs, antibacterial drugs, antidiabetic drugs, sedatives etc. In research, they have developed profound expertise in handling amino acid chemistry; optical resolutions issues; asymmetric synthesis; handling of hazardous reactions such as alkyl lithium/hydrides etc; and heterocyclic chemistry, besides others. It has taken a number of patents on novel processes developed by them. It has not invested on the discovery of novel APIs.

Alembic Pharmaceuticals Ltd, Vadodra

Alembic Pharmaceuticals Ltd **[208-209]** Vadodra, Gujarat is an old pharmaceuticals manufacturing company, which was established in 1907. It is involved in manufacture of pharmaceutical formulations as well as APIs. Alembic is a market leader in India in the basic manufacture of erythromycin and its derivatives. Alembic is a pioneering Indian company and used to manufacture sizable quantities of penicillins and derivatives, cephalosporins, erythromycin and semi-synthetic derivatives of erythromycin from the basic fermentation stage. It also manufacture a number of other generic APIs. The API manufacturing facilities are located at Panelav and Karakhadi in Gujarat. A pharmaceutical formulation manufacturing plant is in Sikkim. Alembic has high reliance on research. Its R&D initiatives are guided by the organisational philosophy of providing affordable high quality medicines for health care. Alembic has state of art R&D Centres at Baroda and Hyderabad. More than 500 Scientists are employed in R&D. It works on developing novel cost-effective processes for generic APIs, and pharmaceutical formulations in the oral solid dosage forms, liquids, Injectable, etc. Presently, Alembic manufactures 39 generic APIs. Alembic has protected multiple number of their inventions by patents **[210]**.

Allastir Private Limited, Chennai

Allastir Private Limited **[211]**, Chennai, Tamilnadu was incorporated **[212]** on 19 June 2017. It is a R&D based technology development company for the manufacture of generic APIs. At present, more than a dozen of generic APIs are being manufactured; several other generic APIs

are in the development. Besides the manufacture of generic APIs, the company also manufactures a large number of formulations which are dispensed in different finished forms as tablets and capsules.

Anjan Drug Pvt Ltd., Chennai

Anjan Drug Pvt Ltd.**[213]** , Chennai was founded in 1990 by Mr. C Kalaichelvan. It is an integrated pharmaceutical API manufacturing company. The company has two manufacturing units. In the one at Alathur, close to Chennai airport manufacture of certain generic APIs such as valproic acid, sodium valproate, divalproex sodium, gabapentin and magnesium valporate is undertaken, while in the other unit at Gummidipoondi diethyl dipropyl malonate and gabapentin hydrochloride is manufactured. The manufacturing units are c GMP compliant plants. The company is engaged in the development of cost-effective processes for the manufacture of generic APIs. Its bulk APIs are sold internally as well as exported.

Aurobindo Pharma, Hyderabad

Aurobindo Pharma Limited headquartered in HITEC City, Hyderabad, India is an Indian multinational pharmaceuticals manufacturing company. Aurobindo Pharma **[214]** was founded in 1986 by Mr. P. V. Ramprasad Reddy, Mr. K. Nityananda Reddy and a small group of highly committed professionals. The company commenced operations in 1988-89 when they started manufacturing semi-synthetic penicillins at their Pondicherry unit. Later, more manufacturing units were constructed. Aurobindo Pharma became a public company in 1992. At present, Aurobindo is considered to be one of the top API manufacturing companies in the world. Aurobindo Pharma is globally known for production of generic APIs in the category of beta lactams and non-beta lactams. It also manufactures other range of APIs which include anti-retroviral drugs, anti-infectives, cardiovascular drugs, central nervous system products, gastroenterological products, and anti-allergic drugs **[215]**. Its leadership emanates from their own advanced API research house expertise of its research team. Aurobindo Pharma has its sister concern Aurobindo (Datong) Bio Pharma Co Ltd, China which is engaged in the manufacture of 6-aminopenicillanic acid (6-APA) . The production of 6-APA is exported to India and consumed **[216]** at Aurobindo Pharma. Aurobindo Pharma also has their pharmaceutical formulations manufacturing segments. Aurobindo Pharma is not in the development of novel APIs. The company has made several inventions in process developments of APIs and has taken patents **[217]** on multiple of their inventions.

Basic Pharma Life Science Pvt Ltd , Ankleshwar

Basic Pharma Life Science **[218]** Pvt Ltd , Ankleshwar, Bharuch was established in the year 2003 as a partnership firm for manufacturing of Chlorhexidine & Cetrimide. The manufacturing facility was upgraded to comply with c GMP specifications in 2010. At present it manufactures more than a dozen of generic APIs. The company exports its APIs to Middle East, Latin America, Middle and East Asian countries. It has not invested on the development of novel APIs.

Biocon Ltd (Biocon), Bangalore

Biocon Ltd (Biocon), Bangalore is a global biopharmaceutical company with profound interest in the manufacture of generic APIs. Biocon has multiple subsidiary units namely Biologics Biologics, Syngene International Ltd. (Syngene), and Clinigene International Ltd. Biocon was incorporated in the year 1978 as a joint venture between Biocon Biochemicals Limited of Ireland and an Indian entrepreneur Kiran Mazumdar-Shaw. Biocon Biochemicals Limited, Ireland was acquired by Unilever plc in 1989 and merged it with its subsidiary company Quest International. Later in 1998 Unilever entered into an agreement with ICI,UK

to sell its specialty chemicals division of which Quest International was a part; Unilever also agreed to sell its shareholding in Biocon to the Indian promoters. As a result, Biocon became an independent entity from 1998 and thereafter. At that time Biocon used to manufacture different kinds of enzymes. The success of the company emanated from their invention of a solid substrate fermentation, technology, which was scaled up from pilot size to plant level in 2000, enabling manufacture of a wide range of industrial enzymes and other substances cost-effectively. In another major development, by teaming up with Shantha Biotechnics Limited, Hyderabad Biocon had developed the human insulin technology on *Pichia pastoris* expression system in the year 2003. This was an extremely great success.

In 2004, Biocon's Syngene developed and launched new generation human insulin INSUGEN. Biocon thereafter got interested in the development of similar biologics, and in collaboration with Vaccinex Inc, USA entered into the development of a wide range of therapeutic antibody products **[219-221]**. Biocon has also interest in the manufacture of generic APIs. Currently, the company has multiple state-of-the-art manufacturing facilities across Bangalore, Hyderabad and Visakhapatnam **[222]**. It manufactures and sell 26 generic APIs. Biocon is investing a large sum for the manufacture **[223]**of fermentation-based APIs and drug intermediates. A large number of patents **[224]**have been obtained by the company for their inventions which include novel processes for certain APIs. Biocon has interest in the development of novel APIs. The subsidiary company of Biocon, namely Syngene, is involved in certain specialised services which include Discovery Services, Development Services, Manufacturing Services and Dedicated R&D Centres. Through the Development Services, activities such as drug substance development through the processes of drug substance development, drug product development and associated services to demonstrate the safety, tolerability, and efficacy of novel drug candidates are pursued. It is not clear if there is emphasis on own development of NCEs. The company has not declared the development of any novel API, which may be in the pipeline. It has, however, profound interest in the development of similar biologics as well as novel biologics, which are not the subject matter of discussion in this study.

Cadila Pharmaceuticals, Ahmedabad

Cadila Pharmaceuticals, Ahmedabad was established in 1951. The company was started in 1951 by Indravadan A. Modi with his friend Ramanbhai Patel. The company had later split in 1995 into two separate companies, namely Cadila Pharmaceuticals Ltd., Ahmedabad and Zydus Cadila, Ahmedabad; both the companies had established R&D units in Ahmadabad to develop innovative technologies for the manufacture of APIs and pharmaceutical formulations. Cadila Pharmaceuticals has collaborations with a large number of leading Research and Development establishments in India and it appointed the best scientific talents there from, thereby enabling the development of application-oriented technologies based on basic research done at its research establishments **[225].** Cadila Pharmaceuticals after the separation had concentrated on the production of multiple number of generic APIs which include **[226-227]** antibacterial drugs, anti-inflammatory drugs, cardiovascular drugs, antihypertensive drugs, antithrombics, cardiotonics, antidiabetic drugs, antirheumatic drugs, antigout drugs, antiasthmatics, antidepressants, antipsychotics, anticonvulsants, antihistaminic drugs, antiosteopotatic drugs, antiemetics, drugs for treating benign prostatic hyperplasia, iron chelating agents, proton-pump inhibitors and disinfactants. The total number of APIs being manufactured is currently 46 only. The APIs manufactured are in the plant/s of the company where standards of c GMP applicable or equivalent to what have been laid down in EU are maintained. Cadila has taken patents **[228]** on multiple of their inventions. It has not concentrated on the development of new APIs.

Centaur Pharmaceuticals Private Ltd , Mumbai

Centaur Pharmaceuticals Private **[229]** 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 to be tested for the treatment of diabetic foot ulcer. The molecular formula **[230]**of Diperoxochloric acid is Cl_2O_6 and the molecular weight is 166.9 g/mol. Diperoxochloric acid 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 **[231]**on the formulation derived from Diperoxochloric acid . Based on the results of Phase-III trials, the drug was approved for human use in India by the DCGI in 2020. The novel formulation of Diperoxochloric acid was launched by Centaur **[232]** in October 2020 by the trade name WOXHeal and was indicated for the in the treatment of Diabetic Foot Ulcer. Centaur was started **[233]** in 1978 with manufacturing operations in pharmaceuticals. Presently, the company has developed expertise in the whole pharmaceutical value chain including manufacture of generic APIs, generic and branded generic pharmaceutical formulations, Contract Research and Manufacturing Services, Clinical Research, R&D, expertise in regulatory documentation and marketing. Centaur is presently, the largest manufacturer and exporter of psychotropic drugs.

Century Pharmaceuticals Ltd, Vadodra

Century Pharmaceuticals Ltd.**[234-235]**, Vadodra is a pharmaceutical company involved in the manufacture and distribution of generic APIs and finished pharmaceutical formulations. The foundation of the company was laid in the district Panchmahal, Gujarat in 1982 with the aim of manufacturing generic APIs. Dr. Janak Sheth, an alumnus of IIT Delhi is the owner of the company. The company aims at developing cost-effective technologies for the generic APIs for use in human medicine, animal health protection and also in biotechnology area. They also undertake contract research, process development and stability studies. The major revenue of the company comes from the sale of generic APIs. The company manufactures and supplies more than forty generic APIs, and a sizable numbers are exported.

Cipla, Mumbai

The present company Cipla, Mumbai was founded **[236]** by Khwaja Abdul Hamied in 1935 as the Chemical, Industrial, & Pharmaceutical Laboratories. Up to the period of 1960, the progress had been slow but steady. From the decade of 1970 onwards, the company made enormous contributions by concentrating on the development of innovative processes for the manufacture of already known APIs, primarily one of the leading concentrating on import substitution and reduction in the prices. Cipla became known for the supply of a wide range of generic APIs required for the treatment of multiple viral diseases especially the HIV drugs at affordable prices. The company had concentrated on the production of multiple number of generic APIs which include antiviral drugs, antibacterial drugs, antifungal drugs, antimalarial drugs, anthelmintics, cardiovascular drugs, antidiabetic drugs, breathing care and drugs for the treatment of breathing disorders, anti asthmatics, drugs for treating benign prostatic hyperplasia and certain others drugs. It has not invested or concentrated on the development of new **[237]** APIs but has teamed up with Indian national institutes engaged in novel drug discovery research for marketing novel APIs discovered by such institutes. It has claimed to have its API pipeline which consists of more than 75 generic APIs in the therapy areas of Oncology, hepatitis B; hepatitis C; antiretroviral drugs; diabetology; drugs acting on cardiovascular system ; central nervous system; respiratory system etc. It has taken a large number of patents **[238]** on its discoveries and inventions.

Concord Biotech Ltd, Ahmedabad

Concord Biotech Limited **[239-240]** Ahmedabad is an R&D based biotechnology company.

The activities are focused on the fermentation, semi-synthesis as well chemical synthesis based products. The company was established by Dr. Sudhir Vaid in 2000. The existing portfolio of products includes APIs in the therapeutic areas of immunosuppressant drugs, antibiotics, oncology products, anti-obesity drugs, hypolipemic medicaments and certain enzymes used for the manufacture of certain beta-lactam antibiotics. A sizable number of APIs are being exported. Its R&D is focussed on process development through microbial fermentation, semi-synthesis and synthesis. The company has protected a large number of their inventions by patents **[241]**. It has not invested on the development of novel APIs.

CTX Lifesciences, Gujarat

CTX **[242]** Lifesciences, Gujarat is a company, which is involved in the manufacture of generic APIs and drug-intermediates. The company has constructed a c GMP manufacturing facility, which is spread over 38 acres of land located at Sachin, in the district of Surat, Gujarat. The facilities have installations of manufacturing block; quality control establishments; engineering; utilities block; storage for solvents, acids and alkalis ; generator building; R&D block etc. The company was incorporated **[243]** on 05 February 2004. It manufactures about thirty generic APIs, most of which are exported. It has invented certain novel processes, which are protected by patents **[244]** .

Dabur Research Foundation, New Delhi

Dabur **[245]** is an Indian consumer goods company. It was founded in 1884 by S. K. Burman. The company manufactures Ayurvedic medicine and natural consumer products and is one of the fast-moving consumer goods companies in India. Dabur set up its Dabur Research Foundation (DRF) in 1979 which has Headquarters at Sahibabad, Ghaziabad, India. DRF is an Indian contract research organisation which offers **[246]** pre-clinical services in drug discovery and development. In 2003, Dabur established its Dabur Pharma Ltd to separate its pharmaceutical business from other activities. This company develops, manufactures and markets pharmaceutical products which include anticancer products; cardiovascular drugs; antibacterial formulations; anti-diabetic drugs; products used as digestive aids; various oral and injectable finished dosage forms; as well as active pharmaceutical ingredients (API) and drug intermediates. Certain key APIs marketed by the company are alphabetically docetaxel, gemcitabine, irinotican, oxaliplatin, paclitaxel, temozolamide and thalidomide **[247]**. The author along with others together from Delhi University and DRL had developed a novel process of manufacturing pharmaceutical formulations of paclitaxel, its derivatives or analogues entrapped into nanoparticles of co-polymeric micelles constituted of block co-polymers that could entrap these substances. An US patent **[248]**was taken for the invention, which was assigned to DRL. Besides one, several other patents **[249]** have been taken by the Dabur Research Centre to protect their inventions. A German company, Fresenius SE bought a 73.27 per cent equity stake in Dabur Pharma in June 2008 . The parent company Dabur has several other sister companies. No novel API has yet been discovered by the group which has reached regulatory approval.

Dr. Reddy's Laboratories, Hyderabad

Dr. Reddy's Laboratories, Hyderabad is an innovation–driven company which put much of its investment for the development of new chemical entities. Dr. Reddy's Research Foundation **[250-251]**, Hyderabad was established in 1992. They are exploring the development of new medicines especially in areas of anti-cancer drugs, anti-diabetes, cardiovascular drugs and anti-invectives. In mid-1990s and onwards further newer developments started to take place. Thus far, no new chemical entity has come out which has the approval of the regulatory authorities for use as drugs in human therapy. However, the company is engaged in the manufacture of a

large number **[252]** of generic APIs. Dr. Reddy's Lab has secured their inventions through a large number of patents **[253].**

Divi's Laboratories, Hyderabad

Divi's Laboratories **[254-255]** Hyderabad was established in the year 1990 initially as Divis Research Center (DRC) with Research & Development as their prime fundamental activity. Their research is devoted to the development of cost-effective processes for the manufacture of generic APIs. Presently, the company is engaged in manufacture of multiple numbers of generic APIs and nutraceutical products. They also undertake custom synthesis of APIs and intermediates for global innovator companies. Divis has presently a portfolio of 120 products across diverse therapeutic areas. The company has established four manufacturing facilities, which are located at Lingojigudem in Yadadri Bhuvanagiri District near Hyderabad (Telangana) with 11 multipurpose production blocks for the manufacture of certain APIs; an export oriented unit located at village Chippada Bheemunipatnam Mandal about 30 Km from the port city of Visakhapatnam (Andhra Pradesh) on the east coast situated on a 100-acre site; the third one is located at village Chippda and is a SEZ Pharma Unit; and the fourth one is located at the company's Pharma SEZ at village Chippada. It has two subsidiary units namely Divis Laboratories (USA) Inc. in the United States of America and Divi's Laboratories Europe AG in Switzerland, where nutraceuticals products are manufactured. The R&D establishments of the company are located at Sanathnagar Hyderabad and at each of the above Indian manufacturing sites. The Sanathnagar R&D Centre works mainly on projects, which are focussed on custom synthesis contract research for foreign MNC companies. At this site, research is also carried out for the development of cost-effective novel processes for the future generic APIs. The company at present manufactures more than twenty five numbers of generic APIs, several of which are also exported. The company has secured multiple numbers of their processes by patents **[256]**. The company has not invested on the development of novel APIs.

Elder Pharmaceuticals,Mumbai

Elder Pharmaceuticals Ltd **[257-258]** Mumbai was formed in 1989 by Late Jagdish Saxena. The main activities include the manufacturing and marketing of prescription pharmaceutical brands, surgical and medical devices. The products marketed by the company included three main therapeutic segments such as women's healthcare, wound care and nutraceuticals. The company has six manufacturing plants in India and one in Nepal. Like other pharmaceutical companies, it manufactures various dosage forms like tablets, capsules, syrups, injectables, topical creams and ointments. The Saxena family-controlled Elder Pharmaceuticals teamed up with multiple institutions for jointly benefitting each other and was interested in the development of novel APIs and formulations based there from, in the areas of diabetes and anti-inflammatory drugs. However, no novel API came out from their efforts. A small number of inventions were made by the company which were patented **[259]**.In the meantime, the company went into serious financial losses and plunged into more uncertainties.

Elixir Pharma, Ahmedabad

Elixir Pharma **[260]**, Ahmedabad was started in 2009 and the company received the c GMP certification in 2010. The company has expertise in condensation, cyclization, Friedel-Crafts Reaction, Reformatsky Reaction, Grignard reaction, Suzuki Coupling, Borane Chemistry and in handling certain other hazardous reactions utilising hazardous chemicals. It manufactures a small number of generic APIs such as glybenclamide, nalidixic acid and pregabalin.

Emcure Pharmaceuticals Ltd,Pune

Emcure Pharmaceuticals Ltd **[261]**, Pune was

incorporated in April 1981. It is manufacturing pharmaceutical formulations in multiple therapeutic areas including pain management and analgesics, cardiovascular drugs, blood-disorder related therapeutics, anti-HIV drugs, nephrology drugs, anti-infectives, vitamins, minerals, oncology products, antidiabetic drugs and neuroscience therapeutic areas. The company export their products to over 70 countries and have subsidiaries and branch-offices in several countries. Its research is concentrated on the development of products across several platforms including chiral molecules, similar biologics and novel drug delivery systems. The R&D team has more than 500 highly qualified scientists. The R&D team is dedicated to developing novel processes for complex APIs, finished formulations, similar biologics and novel drug delivery systems. It is also involved in the discovery of novel APIs although its main emphasis is on novel process development of generic APIs. A sizable number of patents **[262-263]**have been taken by the company for their inventions including on novel API. However, no novel API has yet been marketed by the company.

FDC Ltd,Mumbai

FDC Ltd **[264]** (FDC), Mumbai the public limited company was the new name selected by the previous company Fairdeal Corporation (Private) Limited, Bombay. Fairdeal was originally created and incorporated as a partnership firm in 1936 by Anand Chandravarkar, a visionary who wished to build a world-class pharmaceutical company. In 1940 Fairdeal was transformed into a private limited company. Fairdeal was the pioneer in the manufacture of Oral Rehydration Salts (ORS) in India. In 1986, Fairdeal was renamed as FDC Ltd. For the production of generic APIs , the company has set up multi-location manufacturing facilities. It has also simultaneously set up manufacturing facilities for pharmaceutical formulations. The production facilities are located at Roha, Waluj and Sinnar in Maharashtra, Verna in Goa and Baddi in Himachal Pradesh. The company manufactures and markets more than 300 products in India and exports many of these to over 50 countries. FDC is focused on the development of cost-effective processes for generic APIs. The company has installed a State-of-the Art facility, for this and has capability of performing cryogenic and hydrogenation reactions. The laboratories are well equipped with high-class LC-MS, HPLCs, UPLC, GCs, IR, Polarimeter, Stability Chamber, Vacuum Drier, Lyophilizer and Chiral Preparatory HPLC instrument. The R&D team has highly qualified Scientists, supported by QC & RA team for Regulatory filings. The company also has R&D facilities for formulations development, as also development of biotech products. Company is presently manufacturing eighteen numbers of generic APIs and several others are in the developmental stage. It has not concentrated on the development of novel APIs but had explored the possibilities of collaborating with institutions for such developments. FDC has protected their inventions **[265]** through patents. It has developed novel formulations using **[266]** known APIs. It has not come out with any novel API so far.

Glenmark Pharmaceuticals Limited, Mumbai

Glenmark Pharmaceuticals Limited, Mumbai was established **[267]** in 1977 by Late Mr. Gracias Saldanha. Glenmark entered the dermatology market in 1979 with the launch of 'Candid cream'. In 1999, Glenmark commissioned Sinnar R&D centre in Maharashtra. In 2001 it diversified to API manufacturing and set up new R&D unit in Mahape, Navi Mumbai in an area of over 1,25,000 sq. ft. Presently, the group manufacture **[268]** and supply over 130 APIs covering multiple therapeutic areas, and that about 75 APIs are being exported. Glenmark is a R&D focused pharmaceutical company having strong interest for the development of novel APIs; over the last 40 years it has worked on serious medical problems especially in unmet needs in

inflammation disorders, respiratory disorders, dermatology therapies and also oncology. It has a strong R&D pipeline of specialty products and innovative molecules. Important new chemical entities include Oglemilast [N-(3,5-Dichloropyridin-4-yl)-4-(difluoromethoxy)-8-(methylsulfonamido) dibenzo[b,d]furan-1-carboxamide] and certain others. The company sold the rights on Oglemilast **[269]** to a Japanese company and the NCE is under research. Glenmark has taken a large number of patents **[270]** to protect their inventions. No novel API, however, has yet been approved for human therapy from the company.

Granules India Limited, Hyderabad

Granules India Limited **[271-272],** Hyderabad is a large-scale vertically integrated pharmaceutical company, which is engaged in the manufacture of a large number of generic APIs. It also manufactures drug-intermediates and finished pharmaceutical formulations. The company was founded on March 18th 1991. The company pursues its business on three segments which include the manufacture of certain generic APIs such as Paracetamol, Ibuprofen, Metformin, Guaifenesin and Methocarbamol as the core business; emerging business which focuses on the manufacture of other generic APIs; and a third segment which focuses on contract research and contract manufacturing. The company has constructed four API manufacturing facilities and one drug-intermediate manufacturing facility in Hyderabad and Vizag. They had acquired Auctus Pharma in 2014, thereby enabling them to add more number of generic APIs to their manufacturing portfolio. Its R&D is focussed on the development of novel processes for the manufacture of generic APIs in the therapeutic categories of anti-retrovirals, anti-hypertensives, anti-histamines, anti-infectives, analgesics, anti-coagulants, anti-fibriotics and platelet inhibitors. The company has secured several of its inventions by patent protection **[273],** but has not invested on the development of novel APIs.

Halcyon Labs Pvt. Ltd., Ahmedabad

Halcyon **[274]** Labs Pvt. Ltd., Ahmedabad is engaged in the manufacture of a number of generic APIs which include products in the therapeutic categories of anticonvulsant drugs, antifungal medication, corticosteroids, macrolides, and others. The total built-up manufacturing facility measures 2864.8 sq. mts. The production facilities conform to c GMP standards. A couple of its bulk APIs is being exported.

Hetero Drugs Limited, Hyderabad

Hetero Drugs Limited (HDL **[275-276]** Hyderabad is one of India's leading manufacturer of generic APIs and the considered to be very large global producer of anti-retroviral drugs. The business of the company includes generic APIs, generic and branded generic formulations, biosimilar products and custom pharmaceutical services. Hetero has presently thirty six c GMP compliant manufacturing facilities strategically located worldwide. Its products encompass major therapeutic categories such as AIDS/HIV, Cardiovascular drugs, Diabetes, Hepatitis, Hepatology, Immunology, Neurology, Nephrology, Oncology, Ophthalmology and Urology. Hetero has a presence in over 126 countries. HDL is the parent company in the Hetero group of companies; the other sister-concerns and connected companies are Hetero Labs; Hetero Research Foundation; Genx Laboratories; foreign subsidiaries such as Camber Pharma Inc., USA; Hetero Europe; and Richmond Labs, Argentina. The company has concentrated in the development of novel processes for the manufacture of generic APIs. It has also invested in novel drug discovery research, especially in anti HIV drugs, anti-viral drugs, diabetes and cancer. However, no new API has yet come out from their efforts.

IOL Chemicals and Pharmaceuticals Ltd, Ludhiana

IOL Chemicals and Pharmaceuticals Limited **[277]**, Ludhiana was established in 1986.They

presently manufactures certain generic APIs in the therapeutic categories of pain management, anti-diabetic drugs, anti hypertensive and anticonvulsants. The APIs include ibuprofen, metformin hydrochloride, lamotrigine, fenofibrate and clopidrogel bisulphate. They also manufacture a number of industrial chemicals. The company has an R&D unit which specialises in the development of cost-effective processes so as to remain competitive. They export their generic APIs to several countries.

IPCA Laboratories Ltd

IPCA Laboratories Limited **[278]**, Kandivali, Mumbai was founded by a group of medical professionals and businessmen in 1949 as 'The Indian Pharmaceutical Combine Association Limited' and later the name was changed to IPCA Laboratories Ltd in August 1964 and to Ipca Laboratories Private Limited in January 1966. The present name **[279-280]** IPCA Laboratories Ltd continues to be the name of the company since August 1988 and became a public limited company since March 1993.Over the years it has undergone many changes and have made substantial progress. Presently the company does business in over 120 countries across the world and manufactures over 350 formulations and 80 generic APIs in various therapeutic segments. The branded pharmaceutical formulations are in the categories of management of pain, rheumatology treatment, antimalarial drugs and hair care therapy. These are dispensed as oral liquids, tablets, dry powders and capsules. The company presently employs about 13900 people across its various locations. IPCA is engaged in new drug discovery and development research. Besides company's own efforts, It is also collaborating with certain national and international research organizations for achieving success. The research emphasis is on finding NCEs for pain-management, cardiovascular drugs and antimalarial drugs. IPCA has obtained a large number of patents **[281]** for their inventions. No new API has however come out from their efforts.

J.B. Chemicals & Pharmaceuticals Ltd, Mumbai

J.B. Chemicals & Pharmaceuticals Ltd (JBCPL), Mumbai was established in 1976. JBCPL has a remarkable past history **[282]**. Initially a partnership firm, Unique Pharmaceutical Laboratories was established in December 1950 which over the years evolved and got transformed in to JBCPL. In August 1985, the name J. B. Chemicals & Pharmaceuticals Ltd was adopted. The company is an integrated, research-oriented, public-listed organisation. The pharmaceutical products are dispensed in various dosage forms like tablets, capsules, lozenges, liquids, creams and ointments, injectables as well as herbal liquids. JBCPL is also engaged in the manufacture and supply of a large number of APIs. Manufacture of bulk metronidazole was an important earlier activity. The company initiated research on NCEs in early 2000 and developed a couple of new compounds for treating inflammation. None of these had reached the novel API approval stage however. A number of inventions were patented **[283]** by the company. On 3 July 2020 in a news item it was revealed that 54 per cent of the equity stake of JBCPL was being acquired **[284]** by the US private equity giant KKR at a price of Rs 31 billion (Rs 3100 crores).

Jubilant Life Sciences

Jubilant Life Sciences (formerly known as Jubilant Organosys), Noida, UP is a large group and has multiple subsidiary companies, some in India and some abroad. The main subsidiary companies **[285]** in India include Jubilant Biosys Limited, Jubilant Generics Limited, Jubilant Pharma Limited and Jubilant Infrastructure Limited. Another couple of companies registered abroad are also the subsidiaries of this company. Jubilant Life Sciences was incorporated in the year 1978. Jubilant Life Sciences Limited **[286]** is an integrated global pharmaceutical and life sciences company. It is engaged in

pharmaceuticals, life science ingredients, drug discovery solutions and manufacture of branded pharmaceuticals. The business of the group **[287]** includes manufacture and sale of a wide range of products and services to their customers across different parts of the world. It manufactures and sale Radio-pharmaceuticals and Allergy Therapy Products and a wide range of APIs. Jubilant Pharma manufactures 27 numbers of generic APIs in therapeutic areas encompassing CVS, CNS, Anti-infective and Anti-ulcerants. The company is also involved in providing contract manufacturing services a wide range of pharmaceutical formulation and APIs.

Jubilant Life Sciences Limited is a part of the Jubilant Bhartia Group **[288]**, Noida, UP. Jubilant Bhartiya is a large industrial group having business in multiple sectors such as Jubilant Life Sciences Limited, Jubilant Food Works Limited, Jubilant Industries Limited and others, employing workforce of around 39,000 employees all over the world. Jubilant Bahrain is a multinational Indian company. The group set up Jubilant Innovation **[289-290]** (India) Limited in November 2007. This company is involved in the discovery of NCEs and novel APIs singularly or in duel-business model mode for co-developing proprietary NCEs, besides working in other areas. This company also provides services to other clients in discovery research. It entered into collaborations with multiple international companies. Its main interest in drug discovery research is multiple areas of cancer therapy. A large number of patents **[291]** have been taken by the company on their inventions. The group has not yet been able to come out with any novel API.

Kothari Phytochemicals,Kolkata

Kothari Phytochemicals International, Kolkata was established **[292]** in 1974. It has a manufacturing unit at Nagari, TamilNadu about 20 KM from Madurai City, where it has a space of about 70 acres of land. The company produces certain generic APIs such as Chlorpropamide, Metformin HCL and Tolbutamide and a sizable number of Phytochemicals. It specializes in the manufacture of herbal extracts, a wide range of Phytochemicals and natural pharmaceutical ingredients. It has an R&D unit also. But company has not invested on the development of novel APIs.

32. Lupin Ltd, Mumbai

Lupin was founded in 1968 by Dr. Desh Bandhu Gupta. He steered the organization to become one of the fastest-growing generic pharmaceutical companies around the world. Lupin is a global pharmaceutical company. Its products-range include medicines in the therapy areas of anti-infective drugs, antidiabetic drugs, asthma treatment, cardiovascular formulations, drugs acting on the central nervous system, drugs acting on gastro intestinal ailments, gynaecology, paediatrics, and non-steroidal anti-inflammatory drug-formulations. The company is also a global leader in the anti-TB drugs and cephalosporins **[293]** . In research, the focus of the company is in the development of innovative technologies to manufacture complex generic APIs, modern biotechnology products and also the development of novel new drug discovery. It is also focused in herbal medicines. The company has multiple R&D sites. No new API has yet been turned out from their research work. Lupin has multiple sites **[294]** of API manufacture and it manufactures and sells **[295]** fifty five numbers of generic APIs. The APIs manufactured are in the plant/s of the company where standards of c GMP applicable or equivalent to what have been laid down in EU are maintained. Lupin has secured its inventions through a large numbers of patents **[296]** .

Mankind Pharma, New Delhi

Mankind Pharma, New Delhi was founded in 1995; it set up its research **[297]** unit at Manesar in mid-nineties. The company has set up its R&D labs pursuing research to develop new medicines including new molecules and novel drug delivery systems in a wide canvas of antibiotics, antibacterial drugs, cardiovascular drugs, anti-arthritics, anti-inflammatory drugs,

steroids, antidiabetic drugs, anti-psychotropic drugs etc. Certain NCEs are claimed to have been developed in the areas of antidiabetic drugs, antiartheritics and others although no new API has yet been approved. In biologics, the company is trying to develop a number of products. The company is manufacturing **[298]** a sizable number of IPR-expired generic APIs.

Marksans Pharma Ltd

Marksans Pharma Ltd **[299-301]**, is a pharmaceutical company, which is headquartered at Mumbai. The company was incorporated in 1992 as a wholly–owned subsidiary of Glenmark Pharmaceuticals, Mumbai through its owners, who were traders in bulk drugs and other substances, operating through their company Tasc Chemical India Pvt. Ltd. Later the owners decided to separate form Glenmark and in March 2003 it became a separate entity and the name was changed from Tasc Pharmaceuticals Ltd. to Marksans Pharma Ltd in 2005. It set up two API manufacturing facilities in Pune to manufacture ciprofloxacin, ranitidine and certain other APIs. However, because of intense pricing pressure and market competition besides availability of such generic APIs from China at cheaper prices, it decided to quit API manufacture but established a high-class R&D unit at Goa to undertake contract research work for process development for complex APIs and formulations thereof. The facility can also be used for out-licensing, which is a strategy many inventing global companies take advantage of, to manufacture experimental drugs with a view to reach the market soon. The company also manufactured a wide range of generic and branded generic pharmaceutical formulations.

Matrix Pharmaceuticals

Matrix Pharmaceuticals **[302-303]** Hyderabad was set up by a Telugu industrialist Nimmagadda Prasad in 2000, who purchased a sick company by the name Herren Drugs & Pharmaceuticals Limited (HDPL) and turned it into a profit-making one. HDPL was incorporated as a private limited company in November 1984 and was in the manufacture of generic APIs Ibuprofen, Sulphamethoxazole (SMX), Norfoxacin and Pefloxacin. HDPL later became sick. Matrix used to manufacture a wide range of generic APIs and it acquired several companies over a period from 2000 onwards .Prasad sold Matrix Pharmaceutical to Mylan Laboratories **[304-305]** USA in 2006. Before Matrix was sold out, it initiated R&D in selected areas for the discovery of novel APIs for treating microbial infection, antiasthma drugs, pain management and antidiabetic drugs. However, no novel API could be invented by the company. Matrix protected its inventions through patents **[306]** .

Meck Pharmaceuticals and Chemicals Pvt Ltd

Meck Pharmaceuticals and Chemicals Pvt. Ltd**. [307]**, Ahmedabad is a manufacturer of generic API's, drug intermediates, nutraceuticals, and certain specialty chemicals. Meck was established in 1992. The company was founded by Mr. Rathin Mehta, a Chemical engineer. The company has five manufacturing units which have facilities for conducting multiple unit operations and unit processes. More than two dozen of generic APIs are being manufactured by the company. Sizable quantities of production are being exported. The company has an R&D unit which is engaged in the development of cost-effective processes for the manufacture of generic APIs, but is not involved in the development of novel APIs.

Medilux Laboratories, Dhar, MP

Medilux Laboratories **[308-309]** Pithampur, Dhar, MP was incorporated on 25 April 1985 and the manufacturing unit was established in 1988. Over the years, they have developed expertise in handling several complex and hazardous chemical reactions in industrial scale such as large-scale acylation and alkylation; Beckmann rearrangement; chlorosulfonation; cyclization

reaction; epoxidation; Friedel Crafts reaction; oxidation and resuction; reductive amination; Sandmeyer reaction; Fries rearrangement; Gabriel synthesis; Mannich reaction; methylation; nitration; halogenation; Knoevenagel Michael reaction, etc. The company manufactures a sizable number of generic APIs, many of which are also exported. Its R&D unit is engaged in the development of cost-effective processes for generic APIs, but company has not invested on the development of novel APIs.

Natco Pharma Limited, Hyderabad

Natco Pharma Limited **[310]** (NATCO), Hyderabad is a vertically integrated and R&D focused pharmaceutical company. Vertical integration implies company owns or controls its suppliers, distributors or retail locations to control its value or supply chain. The company is engaged in developing manufacturing and marketing of finished formulations and APIs. It also undertake contract manufacturing. In the API segment, it has skills and capabilities to develop and manufacture APIs requiring multi-step synthesis and complex skills. The company sells their APIs and formulations locally as well as in multiple companies the world over. At present it has concentrated on the development of generic APIs which are especially used for treating ailments in central nervous system, pain management and cardiovascular disease care. Its R&D interest spans novel and cost-effective process development for generic APIs; development of novel drug delivery system; targeted molecular modelling and rational drug design; hybrid technologies involving fermentation and semi-synthesis; and therapeutic peptide synthesis.

NATCO was incorporated **[311]** in September 1981 as private limited company under the name of Natco Fine Pharmaceuticals Private Limited, which became a public company from 1 July 1992. The name was changed to Natco Pharma Limited in February 1993. The company was converted into a public limited company in December 1994. The company has progressed well and had created new establishments, companies and also undergone mergers with several other own concerns such as Natco Parenterals Limited ,Natco Laboratories Limited and Dr. Karanth Pharma Labs Private Limited all of which merged with Natco Pharma in April 1995. Natco Pharma inaugurated Natco Research Center (NRC) at Sanathnagar Hyderabad in 1997 and launched its Oncology division in 2003. The company has interest in the development of novel APIs. In 2012 Natco Pharma won the first ever compulsory license from Bayer for its patent-protected anti-cancer drug Nexavar for manufacture in India. It also has developed NCEs which are being evaluated against mutated forms of chronic myeloid leukemia (CML), lung cancer, head and neck cancer and breast cancer. It protected **[312]** its inventions by taking patents. No novel API has, however, yet been developed and marketed by the company.

Nicholas Piramal India Ltd,Mumbai

The earlier known Nicholas Piramal India Limited (NPIL), Mumbai, now known as part of Piramal Enterprises Limited (PEL), Mumbai is the flagship company of the Piramal Group led by Ajay Piramal. PEL is a company with diverse business interests in multiple areas such as in financial services, insights and analytics besides pharmaceuticals and healthcare. NPIL in itself has a long history. A company by the name Indian Schering Limited was incorporated on 26 April of the year 1947 under British Schering Ltd. It operated in the therapeutic segments of antibacterial drugs, antidiabetic medicines, cardiovascular drugs, nutritional substances, central nervous system drugs and gastro-intestinal drugs. The name of the company was changed from Indian Schering Ltd to Nicholas Laboratories India Ltd in September of the year 1979.

In 1988 when the company Nicholas Laboratories, Bombay was acquired from Aspro Nicholas by the Mumbai-based Piramal family, the acquired company was renamed as Nicholas Piramal India Limited (NPIL), Bombay in December 1992. In 1991 new manufacturing facilities were installed with US-FDA standards with a view to modernising the company. NPIL started acquisition of a number of companies which included Roche Products,

Bombay in 1993 followed by Boehringer Mannheim India, subsidiary of Boehringer Mannheim AG of Germany in 1996. NPIL had later acquired other organizations, companies and bands which include Hoechst Marrion Roussel's Research Centre, Bombay; Rhone Poulenc India Ltd., Bombay; pharma division of ICI India Ltd., Bombay; and the OTC brand Lacto Calamine of Boot's India Ltd, Bombay. NPIL became **[313-316]** a dominant pharmaceutical company soon. In 2008 Nicholas Piramal India Limited was renamed to Piramal Healthcare Limited. In 2012 Piramal Healthcare Limited was again renamed to Piramal Enterprises Limited (PEL). This name presently continues and the company's pharma business comes under PEL. The pharma business is carried out under the aegis of Piramal Pharma Limited (PPL), a subsidiary of PEL. PPL has manufacturing facilities at Hyderabad and Chennai. These facilities can be utilised by others for their process/product development, bulk API manufacture and also to manufacture finished dosage forms of formulations. The company aspires to be the "Partner of Choice and One-Stop-Shop" for other pharmaceutical companies **[317]**. They also have interest in the development of NCEs and novel APIs. They have access to a large numbers of NCEs, obtained largely through acquisition of erstwhile Hoeshst Research Centre, Mumbai. Nicholas Piramal also secured their other inventions by taking patents **[318]** .However, no novel API has come out from them yet.

Orchid Chemicals & Pharmaceuticals, Chennai

Orchid Chemicals & Pharmaceuticals (OCPL) **[319-321]** is a 100 per cent export-oriented unit (EOU) for manufacture of cephalosporins including Cephalexin and Cephradine antibiotics and connected drug intermediates. The company was incorporated as a public limited company in July 1992. It was promoted by K. Raghavendra Rao and M. Narayana Reddy. The old name of the company which was Orchid Chemicals & Pharmaceuticals Ltd was changed **[322]** to Orchid Pharma Ltd (OPL) with effect from 26 October 2015. OPL has set up manufacturing facilities, which are located at Alathur in Tamil Nadu and Aurangabad, in Maharashtra.

The company exports its products to a large number of countries and later diversified to non-antibiotic API product arena too and also manufacture the API sildenafil citrate. It also manufacture finished formulations. OPL is also engaged in R&D for process development of generic APIs. The company has interest in discovery, development and commercialisation of novel APIs and for this purpose they have teamed up with multiple foreign companies. The main therapeutic areas chosen for novel API development are antidiabetic drugs, antiinfectives, pain management, central nervous system drugs and anticancer drugs. The R&D infrastructure established by the company **[323]** includes independent laboratories for medicinal chemistry, analytical chemistry, molecular modeling, pharmacology & pharmacokinetics and molecular biology. It could develop NCEs in two therapeutic areas namely in anti-infectives and in pain management segments and their discoveries were based on confirmatory microbiological and pharmacological studies. However, it has not yet been able to come up with any novel API. Orchid has protected its inventions through multiple patents **[324]** . Orchid was in financial problem and was among the 28 large corporate defaulters in the Reserve Bank of India's list of debt-laden companies that were referred for insolvency in August 2017. Orchid owed a total of Rs 3,200 crore to a consortium of 24 banks. Dhanuka Laboratories, Gurugram, Haryana took over **[325]** Orchid. It is anticipated that Orchid shall come out of the financial problem under the leadership of Dhumka Laboratories and become a profitable company once again.

Palam Pharma Pvt Ltd, Ahmedabad

Palam Pharma Pvt. Ltd **[326]** , Ahmedabad was set up in 1997. The company manufactures a small number of generic APIs which include dicyclomine hydrochloride, clomiphene citrate, proguanil hydrochloride, and clotrimazole. Palam is not involved in the development of novel APIs.

Panacea Biotec Ltd, Delhi

Panacea Biotec Ltd (Panacea) **[327-329]** Delhi is a company which specializes in the manufacture of a wide range of human vaccines. Panacea was incorporated in the year 1984 initially as Panacea Drugs Pvt. Ltd and later in 1995 got listed as Panacea Biotec Ltd. The company has interest in APIs. The R&D focus of the company is in the development of pharmaceutical formulations active for treating diabetes, infection and gastroenterological disorders, organ transplantation medicines and nephrology and cancer. Its drug-discovery R&D lab is established in Mohali, Punjab. It has collaborated with multiple institutions for accelerating drug discovery research. Panacea Biotec has taken a number of patents **[330]** on their inventions. Panacea has not been able to come out with any novel API so far.

ProVentus Life Scienes ,Chennai

ProVentus Life Scienes **[331]**, Chennai is engaged in the manufacture of generic APIs and drug-intermediates. They also provide contract manufacturing services and research services on process development, scale-up and manufacturing. Proventus was established in 1984 as Cure Kraft Chemicals by a group of technocrats **[332]**. Later, Cure Kraft was acquired by the Chemcrown Group. The Chemcrown Group established in 1961 had started its activities with leather chemicals and expanded later over the years into multiple business facets **[333]** including the manufacture of pharmaceuticals, textiles, speciality chemicals, full-shoes, moulds, medical footwear and real estate. Proventus has its manufacturing facilities at Chennai and is engaged in the production of about sixteen APIs including the veterinary APIs. The company also manufactures a couple of drug-intermediates. A number of its APIs are being exported but it has not invested on the development.

Ranbaxy, New Delhi (Now acquired by Sun Pharma)

Ranbaxy is stated to have been started by Ranbir Singh and Gurbax Singh in 1937 as a distributor of products of the Japanese company Shionogi. Ranbaxy was purchased by Bhai Mohan Singh in 1952. The name of the company was changed to Ranbaxy Laboratories Ltd and was incorporated on 16 June, 1961 in Delhi. After Dr. Parvinder Singh, the son of Bhai Mohan Sing joined the company in 1967, the company underwent a massive increase in scale. Sooner the company got engaged into the manufacture of multiple numbers of medicines, cosmetics, a wide range of pharmaceutical products including a number of life saving antibiotics, synthetic APIs and chemical entities. In 1973 it became a public limited company. Dr Parvinder Singh died of cancer on 3 July1999 at the age of 56 years. Termoil started thereafter in the company. During his tenure, Ranbaxy established its Ranbaxy Research Foundation, which was incorporated in 1985 .The focus was to honor scientific talents in India. Ranbaxy spent considerable sum to invent new drugs and newer pharmaceutical formulations. A number of new chemical entities were discovered although none could reach the stage of commercialisation. They had secured their inventions by taking a large number of patents **[334]**. Ranbaxy was acquired by the Japanese company Daiichi Sankyo in 2008 and later in 2014 Sun Pharma acquired 100 per cent of Ranbaxy **[335-336]**. Presently, Ranbaxy belongs to the Sun Pharma group of industries. Ranbaxy Research Foundation was renamed as Sun Pharma Science Foundation **[337]** in 2016. Sun Pharma also has its own R&D units where research **[338]** is carried out among others on development of new chemical entities (NCEs), active pharmaceutical ingredients (APIs) and novel drug delivery systems (NDDS). Sun Pharma is also a dominant manufacturer of multiple numbers **[339]** of generic APIs.

Reliance Life Sciences, Mumbai

Reliance Life Sciences (RLS) **[340-341]** , Mumbai is part of the Promoter Group of Reliance Industries Limited. RLS was established in 2001. RLS is a research-driven organisation, engaged in developing business opportunities in multiple therapeutic areas including bio-therapeutics, especially plasma proteins, similar-biologics and novel bioactive proteins; pharmaceuticals especially in later-generation ones and generic oncology APIs ; services in clinical research ; regenerative medicine including stem cells therapies; and molecular medicines. Pilot Manufacturing facilities of c GMP standards have been set up for oncology products and hyaluronate injectables. The R&D activities in pharmaceuticals are spread in developing novel processes for generic APIs besides exploring search for novel APIs in the areas of lipase-mediated diseases, cancer and inflammation. RLS secured its inventions through patents **[342]**. No novel API has, however, been reported yet by the company.

Sarabhai Chemicals, Vadodra

In the decades of 1930s and 1940s, Ambalal Sarabhai Enterprises entered into diverse fields of business and inducted newer technologies. Dr Vikram Sarabhai laid the foundation of Sarabhai Chemicals **[343]**, Vadodra. Dr. Sarabhai entered into technical collaborations with multiple international companies. Under his leadership, Ambalal Sarabhai Enterprise Ltd diversified into multiple pharmaceutical companies **[344]** such as Sarabhai Chemicals, S G Pharmaceuticals, Sarabhai M Chemicals, Standard Chemicals and Synbiotics. The group with its all associated companies became the first integrated largest Indian pharmaceutical group in India in late 1970s and early 1980s. The group concentrated on the development of new and innovative processes for the production of already known chemical entities. It produced a large number of antibiotics by fermentation such as the penicillins, streptomycin, tetracyclines and amphotericin –B; synthesis of vitamin-C from D- glucose; a host of synthetic drugs such as phenyl butazone, xylocaine etc. In many respect, like the two public sector units such as HAL, Pune and IDPL, Gurugram, this group ushered the advent of the Indian pharmaceutical industry, of which India is proud of. This group was not in the development of novel APIs however.

Shilpa Medicare Ltd, Karnataka

Shilpa **[345-346]** Medicare Limited, Raichur, Karnataka started its operations as a manufacturer of generic APIs way back in 1987. Earlier, the company was known as Shilpa Antibiotics. Commercial production at Shilpa was started in November 1989 and was incorporated as a private limited company in November 20th 1987. The company was promoted by Mr. Vishnukant C Bhutada and his associates. Shilpa became a Public Limited Company from November 1993. Over the years, the company has grown and presently, the company has multiple establishments for the manufacture of generic APIs, drug-intermediates and finished pharmaceutical formulations. The company also provides development service in new drug delivery systems, manufacture of peptides, biotech products and specialty chemicals and has established an API manufacturing unit at Raichur for manufacturing Oncology and Non-Oncology generic APIs; this unit also provides contract research and manufacturing services. Another generic manufacturing unit at Raichur is a 100 per cent Export Oriented API Unit. Shilpa Medicare has two formulations manufacturing facilities, and both are located in India. Shilpa also has a subsidiary unit by the name Loba Feinchemie GmbH, Vienna (Austria) where some production is carried out. Shilpa carries out research for the development of cost-effective processes for the manufacture of generic APIs

as also novel pharmaceutical formulations. It is also establishing new R&D unit at Bangalore. Presently, the company manufactures more than fifty APIs, many of which are exported. A large number of patents have been obtained by the company, securing their inventions **[347]** .The company has not invested for the development of novel APIs.

Solara Active Pharma Sciences, Chennai

Solara Active Pharma Sciences, Chennai is a generic API manufacturing company **[348]**. The company has multiple numbers of API manufacturing facilities located at Pondicherry; Mangaluru, Karnataka; Cuddalore, Tamilnadu; and Ambernath, Maharashtra. The manufacturing facilities have been built to comply with GMP standards of high order. A sizable quantum of production is exported to USA, Europe and other countries. The company's two R&D units located at Chennai, and Bangalore are devoted to development of cost-effective technologies for the manufacture of generic APIs. It has not invested on the development of novel APIs.

49. Sun Pharmaceutical Industries, Mumbai

Sun Pharmaceutical Industries Limited (Sun Pharma), Mumbai, Maharashtra is engaged in the manufacture and sale of a wide range of pharmaceutical formulations and active pharmaceutical ingredients **[349-350]**. The products include pharmaceutical formulations in various therapeutic areas, such as cardiology, psychiatry, neurology, gastroenterology and diabetology. A wide range of APIs as well as anti-cancer drugs, steroids, peptides, sex hormones, and controlled substances are also manufactured. Sun Pharma was established by Mr. Dilip Sanghvi in 1983 as a pharmaceutical company which started marketing a couple of psychiatry drug formulations with a marketing team of two people. The manufacturing facility was in Vapi, Gujarat where facilities for the manufacture of tablets and capsules were established. The company made substantial progress thereafter. Presently Sun Pharma has established over 40 (API & finished dose) manufacturing sites located in India, USA, Brazil, Canada, Egypt, Hungary, Israel, Bangladesh, Mexico, Romania, Ireland, Morocco, Nigeria, South Africa and Malaysia. The product range manufactured include generic APIs and drug-intermediates, over-the-counter (OTC) pharmaceutical products, anti-retroviral drugs, specialty products of wide range in dosage forms of tablets, capsules, injectables, ointments, creams and liquids. Company's specialty APIs, include controlled substances, steroids, peptides and anti-cancer drugs and products are marketed across 150 countries worldwide. The company has strong focus on R&D and has employed around 2000 research scientists, who are working in their multiple R&D centres. It has developed expertise in synthesis, management of unit processes and unit operations required in manufacturing complex generic APIs. The company also works on the development of New Chemical Entities (NCEs). Further, in specialty formulations development it has expertise in the manufacture of liposomal products, inhalers, lyophilized injections, nasal sprays and controlled release dosage forms. Presently, company manufactures over 200 APIs including warfarin, carbamazepine and clorazepate. A large number of patents **[351]** have been assigned to the inventions made by Sun Pharma.

Suven Pharmaceuticals Ltd,Hyderabad

Suven Pharmaceuticals Limited, Hyderabad was incorporated in 1989 and continued operating by this name up to 2003. The name was changed to Suven Life Sciences Limited and was in operation with this new name up to 2019. Later again in the company decided from January, 2020 to be recognized as two separate companies **[352-353]** namely Suven Pharmaceuticals Limited and Suven Life Sciences Limited. The entrepreneur behind the business is Mr. Venkat Jasti who is a professional Pharmacist specialising in Industrial Pharmacy. The revenue of the Group is earned

by providing a wide range of Drug Discovery and Development Support Services (DDDSS) to global Pharma and Biotech companies.

The Group has installed state-of-art facilities and have well-qualified and experienced team of scientists. The company provides services in chemical synthesis; medicinal and analytical chemistry; in-vitro assay development and screening of NCEs; drug metabolism & pharmacokinetics; CNS pharmacology; toxicology and safety pharmacology; formulation development of NCEs; and others. The Group had teamed up **[354]** with Eli Lilly, USA in 2006 in a collaborative research plan to develop novel molecule acting on CNS. No new API has yet come up from the efforts of the Group. They have taken a large number of patents **[355]** for their inventions. Its earnings **[356]** are essentially from the services provided by it to others.

Symbiotec Pharmalab Limited, Indore

Symbiotec Pharmalab Limited **[357]**, Indore is a research-based company which is engaged in the manufacture of Corticosteroids and other steroid-hormones. In 1995, the company started its operations through R&D and pilot scale process development as well as manufacture in small lots and later in 2004 started its commercial scale manufacturing at Rau. A wide range of corticosteroids are in their generic API production portfolio, which include prednisolone, prednisone, methyl prednisolone, hydrocortisone, dexamethazone, betamethazone and host other products and derivatives. The company also manufacture other range of steroids and has presently two manufacturing units and employ about 1100 people. It exports its generic API products widely all over the world.

Syngene International Ltd,Bangalore

Syngene International Ltd (Syngene), Bangalore is a subsidiary unit of Biocon Ltd, Bangalore. Syngene is a custom research and manufacturing organisation and it supports R&D programmes of sponsors from lead generation to clinical supplies. The company was incorporated in 1993 by several promoters and in March 30 2002 the company's 99.9 per cent equity share was transferred to Biocon and the company became a subsidiary of Biocon. The company initiated its work in CRO services during 1994-1995. Syngene expanded into providing Process Research and Optimization Services during 2003-2004. A new research facility was set up at Boammasandra Bangalore later and in February 2006 it had commissioned new facility at Biocon Park, Bangalore. It also received from Cochin Special Economic Zone, approval for setting up of a SEZ unit. The business model of Syngene includes providing services leading to discovery, development services, services related to manufacturing in c GMP compliant plants and conducting research in dedicated R&D centres. Several foreign multinational units teamed up with Syngene for conducting research in multiple areas of drug development. The annual turnover **[358]** of Syngene exceeded INR 1000 crore by the end of March 2016. The R&D capability **[359]** of Syngene includes proficiency in medicinal chemistry, computational chemistry, synthetic chemistry, *in vitro* and *in vivo* biology, drug metabolism and pharmacokinetics, toxicity studies, peptide synthesis and in multiple areas of complex analysis using advanced research instrumentation. Syngene has protected their inventions by securing a large number of patents **[360]** . It is involved in the discovery of NCEs and novel APIs. No novel API has yet come out from its research.

Torrent Pharmaceuticals, Ahmedabad

Mr. Uttambhai Nathalal Mehta started his pharmaceutical company **[361]** in 1959. Mr. Mehta began his work in pharmaceutical business a medical representative with Sandoz, back in the 1940s and later started his own company. His journey was ardent through multiple initial failures and setbacks. Torrent Pharmaceuticals, Ahmedabad was incorporated on 15 July1972 as a private limited company by Shri Rajnikant C.

Patel and his family members; in June 1982, the company was acquired **[362]** by Mr. Uttambhai Nathalal Mehta. The progress of Torrent was initially slow but steady. At present, Torrent Pharma is the flagship company of Torrent Group and is one of the leading pharma companies of the country, employing over 10, 000 people. Their main pharmaceutical products range include anti-infective drugs, antidiabetic drugs, cardiovascular drugs, formulations acting on the central nervous system , gastro-intestinal drugs, pain management drugs, oncology and women healthcare products. Torrent started acquiring a large number of pharmaceutical companies from India and abroad to strengthen its position especially in the Indian pharma market. Torrent manufactures a large number of generic APIs **[363].** Torrent Pharma has its R & D Centre **[364]** at Bhat near Ahmedabad . Research work is carried out in a wide range of disease area such as cardiovascular diseases; metabolic disorders and diseases; diabetes; chronic inflammatory diseases like inflammatory bowel disease; chronic obstructive pulmonary disease; and asthma. Development of new and effective pharmaceutical formulations is the main aim. Formulation development is also carried out in oncology, dermatology, ophthalmic formulations, etc. New chemical entities are being developed for use as new APIs. It has generated a large number of patents. No new API invented by the company has yet been introduced into the market. A large number of inventions have been made by the company as is revealed from the patents **[365]** taken by them.

USV Pvt Ltd, Mumbai

USV Private Limited **[366-368]**, Mumbai is a private Indian multinational company, which was incorporated on 25 August 1961. Presently, the company operates across 65 countries. The company was founded by Vithal Balkrishna Gandhi. The company was started as a joint venture with USV&P Inc. USA, a subsidiary of Revlon. Presently, the products of the company include multiple numbers of generic APIs, a wide range of pharmaceutical formulations, peptides and similar biologics. The company manufactures and sells 27 numbers of generic APIs, which are available internally as well as exported. It has strong emphasis on R&D; the work carried out is on the development of novel processes for the manufacture of the generic APIs, synthesis of commercially valuable peptides, novel pharmaceutical formulations and the development of technologies for the manufacture of similar biologics. It has taken a number of patents **[369]** on their inventions. It has not invested on the development of novel APIs.

Unichem Labs Ltd., Mumbai

Unichem Labs Ltd., Mumbai was founded by Late Mr. Amrut Mody. It produces and sells pharmaceutical formulations covering the therapeutic areas like gastroenterology, cardiology, diabetology, psychiatry, neurology, anti-bacterial drugs, anti-infectives and pain management formulations. Production of multiple numbers of generic APIs is a core strategic business of the company. For the manufacture of generic APIs, they have three state-of-the-art manufacturing sites across India. The APIs manufactured are in the plant/s of the company where standards of c GMP applicable or equivalent to what have been laid down in EU are maintained. Their generic API production range includes over 30 bulk drugs. The R&D facilities of the company include provisions for the development of technologies for the synthesis of generic APIs through non-infringing routes; development of Novel Drug Delivery Systems (NDDS) and a Biotech facility for developing biotech and biosimilar products **[370]**. A large number of their inventions in drugs have been protected by the company through patents **[371]**. The company has not invested on the discovery of novel APIs but they teamed up with Indian national institutes engaged in novel drug discovery research for marketing novel APIs.

Varahi International, Ahmedabad

Varahi International **[372]**, Ahmedabad was set up in 1997 by the entrepreneur Mr. Indravadan Raval in an area of 3000squarw yards, initially manufacturing various dye intermediates and dye-chemicals; in 2007 they diversified into the manufacture of generic APIs. The pharmaceutical plant was c GMP compliant. The expertise in chemical synthesis included condensation, hydrolysis, oxidation, nitration, sulphonation, hydrolysis, reduction, fusion, acetylation, benzoylation etc. More than a dozen of generic APIs, certain excepients and a couple of drug intermediates are being manufactured by them.

Vasudha Pharma Chem Ltd, Telangana

Vasudha Pharma Chem Ltd **[373-374]** ,Hyderabad, Telangana, is a public limited company , which was incorporated on 20 December 1994. The company was promoted by a team of accomplished technocrats who had profound experience on the manufacture of a wide range of bulk drugs and had insight on the Indian pharmaceutical industry. The chief promoter was Mr.M.V Rama Raju. The company is presently engaged in the manufacturing of a large range of APIs, and drug intermediates, which are catered to Indian market as also exported to many countries. They manufacture a wide range of generic APIs , of which their manufacture of piperidone and piperidine derivatives are most significant.The company has presently five manufacturing facilities at various location in India : unit-1 is at , Jeedimetla, Hyderabad; unit-2, unit-3 and unit-4 are at different locations at Jawaharlal Nehru Pharma City Parawada, Vishakhapatnam; and unit-5 is at Atchutapuram, Rambili Mandal, Vishakhapatnam. The manufacturing units comply with the c GMP standards. The company has also set up a pellets manufacturing facility where generic APIs, manufactured in bulk are transformed into pellets, thereby the APIs become more potent and become more bio-available when converted into solid dosage forms such as tablets and capsules. The company has developed manufacturing processes for more than forty numbers of generic APIs of which about twenty numbers are offered as drugs of certain pharmaceutical standards, while others are available as technical packs. Nearly a dozen are being exported. The R&D of the company is focused mainly on the development of cost-effective processes for the manufacture of generic APIs and drug-intermediates as also bulk-APIs converted into novel pellets.

Wockhardt, Mumbai

Wockhardt, Mumbai was founded by Dr. Habil Khorakiwala in 1967.The Group is presently a leading research-based healthcare enterprise with presence in the fields of pharmaceuticals, active pharmaceutical ingredients (APIs), biotechnology including vaccines and super specialty hospitals **[375]**. Wockhardt has invested a sizable sum for the development of new APIs .The Company has developed a number of lead molecules which are mainly in the area of anti-infectives; these are at various stages of clinical investigation; no novel API has yet been approved. The company presently manufactures five numbers of generic **[376]** APIs; the APIs manufactured are in the plant/s of the company where standards of c GMP applicable or equivalent to what have been laid down in EU are maintained. Wockhardt has secured its inventions through a large number of patents **[377] .**

ZCL Chemical Ltd, Mumbai

ZCL Chemical Ltd (ZCL) **[378]**, Mumbai is a 100 per cent Export Oriented Unit (EOU) engaged in the manufacturing and exports of advanced drug intermediates and APIs. They also undertake contract manufacturing of APIs and drug intermediates. Formerly, the company was named as Zandu Chemicals Ltd. ZCL was established in 1991. It has its state-of-the-art US FDA successfully inspected facility located in the industrial park of Ankleshwar, Gujarat. The products manufactured are mainly in the

therapeutic areas of CNS, ARVs and controlled substances. At present, the company claim to have developed technologies for the manufacture of twenty four generic APIs and several others are in the developmental stage. ZCL has taken a number of patents **[379]** on their inventions. It is not engaged in the development of novel APIs. Its expertise can be utilized by others for large-scale manufacture of novel APIs.

Zydus Cadila [Cadila Healthcare]

Zydus Cadila headquartered in Ahmedabad, pursues R&D activities **[380]** in new chemical entities, biologics, vaccines and niche pharmaceutical technologies. Zydus Cadila is a research-based pharmaceutical company. Its research-based product range includes NCEs, vaccines, similar biologics and many more. Zydus Cadila is presently a leading Indian Pharmaceutical company. Products marketed comprise pharmaceutical formulations, active pharmaceutical ingredients, biotechnological products, animal healthcare products as also wellness products.

In 1995, after the group was restructured, Cadila Healthcare was formed under the aegis of the Zydus group. Zydus Cadila invented one new API for treating diabetes as discussed earlier. The company is focused on developing novel antidiabetic APIs. The Zydus Cadila group has more than 30 manufacturing plants worldwide including in India, Germany, Brazil & USA; the company employs over 15,000 people all over the world. Cadila Health Care Ltd of the group manufactured generic APIs. The API manufacturing activities include generic bulk drugs including investigational bulk drugs, drug intermediates and specialty chemicals. The number of generic APIs manufactured **[381]** is presently twenty six and the APIs manufactured are in the plant/s of the company where standards of c GMP applicable or equivalent to what have been laid down in EU are maintained. The company has secured its inventions by patent protection **[382]** in multiple areas of its research in pharmaceutical substances.

V

Major Generic Drugs Manufactured and Exported from India

On the basis of the study of the generic APIs manufactured by the Indian companies and on studying the letters of written confirmation issued by the Central Drugs Standard Control Organization (CDSCO) under Directorate General of Health Services (DGHS), Ministry of Health & Family Welfare (MOH&FW), Government of India as available on the net on major exporters of generic APIs, a list of such drugs was prepared as can be seen at Annexure Table 3, which show the generic APIs which are being exported from India.

As many as 669 generic APIs have been identified and placed in the Table-3 of the ANNEXURE.

These 669 generic APIs have been classified, based on the identification of the curative and remedial applications of these drugs, into twenty therapeutic categories as shown in the ANNEXURE, and data on exports of each generic API falling in those categories were collected, to the extent these were available. The data obtained as published by the Indian Government based on the HS CODE were compiled and rearranged under the twenty therapeutic categories, as has been placed in Table-4 of the ANNEXURE. On the basis of analysis of the exports data, it was revealed that the information on exports of generic APIs from India, using HS CODE could be captured to the extent of about 91% of the total bulk API exports, in value terms.

The manufacture and export of a large number of generic APIs are indicative of high levels of skills in handling a wide range of chemical and biochemical reactions and operations in industrial scale, which provide the major contributions towards value addition besides usage of skilled man-power at comparatively lower salaries and wages.

While the above list of generic APIs being exported is exhaustive, a closer scrutiny reveals that many of the APIs are not exported in sizable quantities. The list also contains a large number of phyto-pharmaceuticals which are currently used in limited quantities as more potent generic APIs have been discovered as alternatives for therapy. A couple of generic APIs are also listed in the table which are being imported also, which happens as a pure business endeavour depending upon the timing, the policy situations, the partnering between the exporting and importing companies and other business opportunities exiting at the time of clinching a business deal. By discounting such products, the generic APIs exported with high value addition or in comparatively higher volumes would be less than 600 in numbers. Other information worth noting is that a large number of the APIs

exported belong to the therapeutic groups of oncology drugs; cardiovascular drugs including those required for management of hypertension, cholesterol reduction and other heart diseases; pain management including those required for musculoskeletal pain, analgesics, migraine treatment and arthritis; infectious disease treatment especially the anti-viral and anti-fungal drugs as also certain bacterial infection; drugs for the treatment of auto-immune diseases including rheumatoid arthritis, Crohn's disease, ulcerative colitis, psoriasis and psoriatic arthritis; treatment of erectile dysfunction ; and those required for treatment of mental illness.

Evidently, it was also observed that the Indian API manufacturers had not paid much attention for the development of novel APIs. It is already known that the development of novel APIs are very time consuming, extremely costly and bear high financial risks. The chances of a successful outcome are very low. The present business environment is extremely competitive and the profit-margins from manufacture are low, which do not ensure generation of sizable surpluses for deployment in R&D for such purposes, although if a jackpot drug is discovered, the returns are very high till the time the novel APIs are protected by strong IPRs. It requires to be explored what policy intervention can be made and business environment can be created at national level to enthuse the Indian industry to invest and concentrate on the development of novel APIs.

VI

Initiatives by Indian Government for Inventing Novel APIs

The Government of India through various scientific departments of the Ministry of Science and Technology has put concerted efforts to promote the development of drugs and pharmaceuticals industry including the development of a wide range of APIs, especially in the public private partnership mode (PPP) mode. The Table 2 summarises the major efforts made by the government in this direction along with years when each inventive policies and plans were initiated.

TIFAC

The Department of Science and Technology (DST) was set up **[383-384]** as a department under the Ministry of Science and Technology by the government in May 1971 to promote newer areas of science and technology through

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

Source: Author's compilation.

various means including funding support and creation of autonomous institutions **[385].** The Technology Information, Forecasting and Assessment Council (TIFAC) was setup in 1988. TIFAC was mandated to work to assess the state-of-art of technology and set directions for future technological development in India in important socio-economic sectors in the form of reports and documents **[386]**. In close association with the industry, TIFAC continues to strive for forecasting of technology development in the country by leveraging technology innovation through sustained and concerted programmes. TIFAC had prepared the Technology Vision 2035 document and other documents of Technology Roadmaps in 12 thematic areas namely, Education, Medical Science & Health Care, Food and Agriculture, Water, Energy, Environment, Habitat, Transportation, Infrastructure, Manufacturing, Materials and Information & Communication Technologies. Since 1988, TIFAC has produced several reports of technology assessment and technology foresight. In the Report **[387]** 'Active Pharmaceutical Ingredients: Status, Issues, Technology Readiness and Challenges' prepared by TIFAC in July 2020, several noteworthy suggestions have been made as summarized below:

- In the existing competitive global environment, requiring creation of conditions of equal level playing grounds there are possibilities that certain essential API may be unavailable or may be in short supply. Taking note of such situations, there is a need to stockpile certain generic APIs which are required for the manufacture of formulations used to treat critical illness.
- There is a need to establish bulk drug manufacturing parks where common facilities may be created for the management of factory effluents, and have central facilities for power and steam generation as also facilities for the recovery of solvents from processed wastes generated from plants operating the manufacturing parks. Such manufacturing parks would ease the setting up of clusters of industries, because of which common facility developments would not only be easier but would also be economically viable.
- For the development of novel APIs, centres of excellence for API development be established with close cooperation between academia and industry.
- Portfolio of pharmaceutical industries may be aligned towards the development of therapies for chronic diseases which include cancer, cardiovascular diseases, respiratory diseases, antidiabetic drugs, and drugs required to treat mental disorders.
- For the successful fructification of "Atma Nirbhar" Bharat, the Indian Public Sector Enterprises and the public-funded research institutes be revitalised.
- Appropriate attention to these recommendations is necessary and policy measures need to be taken to further strengthen the generic APIs producing Indian industry. But more is needed to enable India to invent novel APIs and become a dominant global player in novel API discovery research.

Drug and Pharmaceuticals Research Programmes of the Government

During the period 1994-95, the DST mounted a programme **[388]** on drug development. The programme was essentially for: promoting collaborative R&D with the objectives of synergising the strength of publicly funded R&D institutions and Indian Pharmaceutical Industry; promoting and creating enabling infrastructure, mechanism and linkages for novel technology development for manufacturing drugs; promoting skill development; and enhancing India's self-reliance in drugs and pharmaceuticals especially in areas critical to national health requirements. For availing of the benefits from the programme, an agreement amongst the collaborating parties specifying the rights and obligations and terms and conditions of the DST grant is essential. The terms and conditions include ownership of intellectual property generated in the project on agreed terms and review of progress of the projects.

In this scheme, 30 per cent of the institutional component of the recurring expenditure is to be met by the collaborating industry. Industry can obtain soft loan up to 50-70 per cent of the total project cost and the loan shall attract interest of 3 per cent on diminishing amount and repayable in 10 years. Industry developing drugs for treating neglected diseases like tuberculosis, malaria, Kala-azar, filariases etc receive more liberal supports.

TDB

The Technology Development Board (TDB) was constituted **[389]** under an Act of the Parliament with effect from September1, 1996 as a statutory body of DST.TDB provides financial assistance to Indian industrial establishments for the development and commercial application of indigenous technologies, or adapting imported technologies to wider domestic applications. The objective is to make the weak zone of technology development stronger and commercialisation easier. TDB supports industries by providing Venture Capital (VC) to SMEs either directly or through VC institutions.TDB has also provided financial assistance as grants to Technology Business Incubators (TBIs) and Science & Technology Entrepreneur Park (STEPs) under Seed Support System for Start-ups in Incubators to incubate innovative technological ideas and to graduate them to successful commercialisation. Supporting entrepreneurs involved in the development of drugs and pharmaceuticals including APIs were also within the preview of TDB support. However, the support system was mainly directed towards SMEs.

NMITLI

In 2000-'01, Government of India initiated an R&D programme named as the New Millennium Indian Technology Leadership Initiative **[390]** (NMITLI) in Public-Private Partnership mode. The Council of Scientific & Industrial Research, New Delhi is responsible for the program. The program continues to date. Thus far NMITLI has developed several projects in diverse areas such as in drugs & pharmaceuticals, biotechnology, bio-informatics, chemicals, materials, information technology, energy, weather forecasting and leather technology.

OSDD Programme

A CSIR-led Team India Consortium with global participation was created to support research on a collaborative drug discovery platform on neglected tropical diseases. The initiative is known as the OSDD programme **[391]**. OSDD functions by bringing together experts from diverse backgrounds to focus on discovering and developing affordable drugs for tropical infections.

SBIRI Initiative

The DBT had launched **[392]** in 2005 the programme of the Small Business Innovation Research Initiative (SBIRI) scheme to boost Public-Private-Partnership (PPP) efforts in the country. SIBRI efforts were aimed at strengthening those existing private industrial units whose product development is based on in-house innovative R&D; encouraging other smaller businesses to increase their R&D capabilities; creating opportunities for starting new technology-based businesses by science entrepreneurs; and stimulating technological innovation. The objectives of SBIRI have been to provide support for early stage, pre-proof-of-concept research in biotechnology by industry; to support new indigenous technologies particularly those related to societal needs in the healthcare, food and nutrition, agriculture and other sectors; and to nurture and mentor innovative and emerging technologies/entrepreneurs, to assist new enterprises to forge appropriate linkages with academia and government. Supporting and stimulating research within the ambit of SBIRI for the development of novel APIs was almost impossible as developing novel APIs requires large sums of investment which are not feasible in the environment of smaller businesses set-ups.

Implementation of SBIRI schemes are presently carried forward and implemented through Biotechnology Industry Research Assistance Council (BIRAC) programs.

BIPP

The Government of India from the Department of Biotechnology (DBT) had also set up a program by the name Biotechnology Industry Partnership Programme **[393]** (BIPP). The Programme was to be implemented in partnership with industries to support path-breaking research in frontier futuristic biotechnology areas having major economic potential and making the Indian industry globally competitive. Novel APIs of biotech origin would also receive support from this initiative.

BIRAC

The DBT had set up another programme through an Interface Agency by the name Biotechnology Industry Research Assistance Council **[394]** (BIRAC) to strengthen and empower the emerging Biotech enterprise to undertake strategic research and innovation, addressing nationally relevant product development needs. The initiative was not meant particularly for novel APIs but development of biotech-based APIs would also be supported by the BIRAC.

BIG Programme

BIRAC initiated the Biotechnology Ignition Grant (BIG) programme to foster generation of ideas with commercialisation potential; upscale and validate of proof of concept; encourage researchers to take technology closer to market through a start up; and stimulate enterprise formation. It is a scheme of small monetary value when assessed in the context of developing novel APIs. In this scheme, the successful BIG Innovators receive up to Rs 50 lakhs (USD 70,000 approx) for research projects that have the potential of commercialisation; the duration is up to 18 months. The BIG programme is implemented **[395]** by BIRAC through multiple designated Indian institutions which have partnered with the program.

CRS Initiative

In January 2013, BIRAC announced for the first time the creation of the scheme by the name Contract Research and Services Scheme **[396]** CRS), which is intended to provide support to academia in the form of grant-in-aid for validation of the Proof of Concept (PoC) by an Industrial partner in India. The CRS scheme supports the interaction between research entities, namely the academia and the industry. If the academic institutions have generated or have pre-existing scientifically established leads, they could seek financial support for further research or validation of processes with industry partners within a time frame. For such projects the academic partners can be supported through grant-in-aid for validation of Proof of Concept at their site or for contract research outsourced from a collaborating company.

All the above programmes, schemes and projects of DST, CSIR and DBT had made noticeable impact in promoting research, technology development, and industrialisation through SMEs in the country in developing the drugs and pharmaceuticals industry.

For promoting the Indian Pharmaceutical Industry, Ministry of Chemicals and Fertilizers, Department of Pharmaceuticals **[397]** has been the forerunner in formulating, announcing and implementing all the policies which have been the guiding directions for the industry to follow and prosper in the whole gamut of its multiple components including the production of generic APIs. Multiple programmes and policies including S&T policies implemented specially through scientific departments including DST, CSIR, DBT and others had, over time made India a global player **[398-399]** in the generic drug industry. In 2014 an independent assessment of the two grant programmes of the DBT namely the SBIRI and the BIPP programmes were carried out based on online surveys of 80 firms. It was

concluded that there was ample evidence that these two programs were stimulating R&D as well as efforts to commercialize biotech products and services in the country. The programmes were therefore considered to be successful **[400]** from these considerations. However, no novel API came out from these multiple endeavors.

Novel Drugs: Marine Sources

Prior to these efforts, the Government of India had instituted another one novel programme from the Ministry of Earth Sciences **[401]** to Indian marine resources for the discovery of novel drugs. The Ministry of Earth Sciences had instituted a programme in 1990 under the leadership of Central Drugs Research Institute (CDRI), Lucknow and involving besides CDRI another fourteen 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, Chenna; and (n) Central Marine Living Resources & Ecology, Kochi. The Consortium formed by bringing together the 15 institutions and universities across the country was thought to be useful and productive as the cross-institutional collaboration and the leveraging of human resources from different environment, was thought to integrate ideas from multiple thought processes and efforts to result in productive outcome.

The three main objectives of the consortium were: (1) bio-prospecting of marine organisms occurring in Indian waters; (2) drugs discovery; and (3) drug development with state-of-the-art facilities proposed during the XII Plan Period(2012–17). The exploration of scientific investigation included: collection of new organisms from coastal and offshore (manned submersible); repeat collection of active samples for confirmation of activity, etc; large scale collection of active materials for follow-up studies; characterisation and structural determination, synthesis of active materials base on patentability and commercial value/merits; expansion and up gradation of "in-vitro" and "in-vivo" test models for biological screening will continue; strengthening of information technology using data base and other facilities will continue; and HRD training in bioassay, chemical analysis, IPR and Benefit sharing. During almost the last three decades of research, the efforts have resulted in the identification for four major products, namely an anti-hyperglycemic product(CDR-134-D-123), an antihyperlipidemic product(CU1-002) product, an anti-hyperglycemic-cum-anti-hyperlipidemic product (CDR-134-F-194) and an anti- diarrhoeal product (CDR-134-D125). None of these products have reached the stage of approval for use as an API. In the mean time a sum of more than Rs 200 crore must have been spent as the budget for the project from 2012-'13 to 2016-'17 was Rs 200 crore. Marine reserves and marine environment have been considered as a promising source of natural products, novel molecules, and drugs of therapeutic use. Consequently, the screening for active natural products has been pursued utilising multiple numbers of large and rapid random screening methods. The screening has been directed towards search for novel molecules having antimicrobial properties such as antibacterial, anti-fungal, antiprotozoal including antimalarial properties. Search has also been directed towards finding novel molecules having anti-inflammatory properties and analgesics. In furtherance, search is conducted to obtain anticancer drugs, neuroprotectives, and immunomodulators. India has over 8000 km of coastline with clusters of marine habitats. India has rich diversity of mangrove forests, coral

reefs and inter-tidal rocky, muddy and sandy shores. Consequently, it has been surmised again and again that India should venture into acts to explore the potential of Indian marine habitat especially for discovering new drug molecules. However, the multi-institutional efforts put forward during the long period of nearly three decades yielded very little in terms of discovery of novel APIs.

There is much justification to ponder why the results were not exciting in the context of novel drug discovery from these multiple efforts. No novel API has yet come out from any of these government programmes. Indian discovery of novel active pharmaceutical ingredients during the period from 1972 to 2014 was compiled **[146]** and published in 2016. This one is a more exhaustive review and current. It is anticipated that Indian history on the discovery of novel APIs would be enriched from the information and analysis provided in this study.

Modern Biotechnology Products Emerging From India

With the emergence of modern biotechnology and newer tool in recombinant DNA technology, the churning out of complex biological molecules, especially the bioactive therapeutic proteins and enzymes became easier. In the meantime success in the development of novel APIs from NCEs started becoming costlier from 1980s onwards for various reasons, but particularly because the regulatory authorities wanted to be satisfied more on the safety as well as efficacy of novel NCEs, before approving them as novel APIs.Consequently, research attention started getting diverted towards biotech drugs utilizing recombinant DNA technology from early 1990s, as mentioned earlier. New private companies appeared in the horizon showing interest in modern biotechnology products. The forerunners showing interest for the first time included Transgenes Biotek Ltd., Hyderabad; followed by Shantha Biotechniques, Hyderabad; Bharat Biotech, Hyderabad; and many others thereafter. Initial interest evinced was for the manufacture of recombinant DNA-based hepatitis-B vaccine antigen, expressed in various kinds of genetically modified yeast hosts.This was in early 1990s.The Department of Biotechnology (DBT) of the India Government had played a key role in stewarding such companies by developing rules and procedures for handling such products as these were new products for humankind and people had apprehensions on using such products in human medicine and required evaluation for safety, including environmental safety as well as human and animal health safety. India promulgated laws, rules and procedures through the Ministry of Environment and Forests to deal with such products. DBT served as the scientific body to examine, evaluate and recommend safe use of recombinant DNA-based products in the country. Following the interest evinced by certain companies for the manufacture of recombinant hepatitis B vaccine, several other companies already operating in India in conventional biotech products also came into prominence from late 1990s as these companies became interested in recombinant DNA-based products.The major companies included Biocon, Bangalore; Serum Institute of India, Pune; Zydus Cadila, Ahmedabad; Cadila Pharmaceuticals, Ahmedabad; Intas Biopharmaceuticals Pvt Ltd , Ahmedabad; Wockhardt Ltd, Mumbai; Indian Immunologicals, Hyderabad; Bioogical E Limited., Hyderabad; Bharat Serums and Vaccines Limited, Mumbai; Panacea Biotec Ltd, New Delhi; and some others.

After initial interest was evinced towards the development of technologies for the manufacture of recombinant HBV vaccines, focus was shifted towards developing technologies for the production of other recombinant products which include granulocyte-colony stimulating factors,erythropoietin,interferon alpha 2b and pegylated interferons, epidermal growth factor, streptokinase, human insulin and multiple monoclonal antibodies over a period of time. None of these biotech-products was an original discovery from India which developed and adopted technologies for the manufacture of these substances and several others over the years and gradually became stronger. In this

VII
The Way Forward

The above is a brief account of Indian contributions to the discovery of new APIs. The number of new chemical entities approved and used as new APIs were only 16 which are Urea stibamine; Methaqualone; Enfenamic acid; Hamycin; Centimizone; Centbutindole; Ormeloxifene ; Centpropazine; Centbucridine; alpha, beta-Arteether ;Bulaquine; Chandocuronium iodide ; Nitroxazepine ; Amoscanate ; Saroglitazar; and Diperoxychloric acid. Peruvoside is a cardiac glycoside isolated from matured fruits of ThevetianerifoliaJuss . Gugulipids are extraxted and isolated from Guggul, an oleoresin obtained by tapping and injuring the Commiphoramukul tree. Bacosides are dammarane-type triterpenoid saponins isolated from Bacopa monnieri, a medicinal Ayurvedic herb which has been in use in Indian system of medicine to sharpen intellect and attenuate mental deficits. Consap is a sterile contraceptive cream produced from the saponins obtained from soap nuts of the plant Sapindusmukorosii (commonly known as Reetha in NorthIndia). DalZbone is a product developed from the leaf extracts of Sheeshamtree (Dalbergiasissoo). Among the 16 synthetic APIs, formulations based on the six APIs namely Ormeloxifene or Centchroman (Trade Names of formulations: Chhaya, Saheli, Novex-DS, Centron, and Sevista), Alpha, beta-Arteether (Trade name of formulation: E-Mal); Bulaquine (Trade name of formulation sold with chloroquin : Aablaquin), Nitroxazepine (Trade name: Sintamil); Saroglitazar (Trade name of formulation: Lipaglyn); and Diperoxochloric Acid, (Trade name of formulation: WOXHeal) are presently (February 2021) available in the market.

Three of these products are from a National Laboratory, one from a MNC and two from the Indian private companies. The reasons why only a very small number of novel APIs and their formulations discovered in India from the Indian National Laboratories and Public Funded Institutions are not presently in the market, are not quite clear. The indications for which some of these novel APIs are approved are still relevant in medicine. The products such as Enfenamic acid; Centimizone; Centbutindole; Centpropazine; Centbucridine; and Chandocuronium iodide were marketed by certain Indian companies who had procured the technologies from the National Laboratories and Public Funded Institutions. It appears that the Indian companies could not capture the relevant markets in India. There are no indications if adequate efforts were made for overseas marketing of these products. The author is of the view that unless such products are also got approved in the developed country markets, the potential of sale of such products cannot be fully determined. This point need to be kept in mind for marketing novel APIs and their

formulations when newer developments take place in India. Hamycin, a polyene antifungal product developed by Hindustan Antibiotics Ltd (HAL), Pune also disappeared from the market because HAL became sick and had to discontinue its fermentation production activities.

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 the key role to discover and invent. Inventors are a separate class of people who are to be incessantly encouraged to remain focused in their tasks by providing all the necessary amenities and supports. Their efforts bear fruits when they receive all round supports. The path of 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 and high throughput screening techniques, molecular biology, protein crystallography and computational chemistry, knowledge of physiological mechanisms of disease and many more. Novel API discovery approach often starts from a rationally argued hypothesis to design new chemical entities, proceeds through multiple mechanistic approaches and makes a start. To reach the end with a successful novel API requires involvement of multiple actors. It is no more possible to invent or discover a novel API on single-handed approach and using traditional techniques of drug discovery.

For a country of Indian magnitude, the number of novel APIs discovered is indeed quite 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 in the discovery of novel APIs.

Indian pharmaceutical industry including the generic APIs

On the other hand, India made phenomenal progress in innovation in the whole area of production of cost-effective generic APIs and pharmaceutical formulations manufactured there from. The reasons for these are many. Firstly, 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 Indian private sector, strongly promoting efforts of import substitution. In the meantime, the global social and economic structures changed, moving from socialistic pattern to capitalistic patterns.

The political will and the government intentions in India were to be tuned with the global change, and from 1991 after India resorted to 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 innovative new technologies were 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. 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 in 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 monitory 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.

It needs to be emphasized in this context that since independence of India, the multiple policy incentives promulgated by the Indian government were primarily to put efforts towards developing alternate processes for already existing APIs. The attention and emphasis on the development of new chemical entities for use as novel APIs were meager, primarily due to inadequate availability of research infrastructure, resources and trained man-power. Further, there were imposition of price controls and later, the introduction of a dual-pricing system for active pharmaceutical substances. These policies during the later years 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 wasn't enough surpluses left for allocation for major developmental efforts or even basic research.

Indian policy issues over the years

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 and time. Basic research required 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. Study of the world economic developments during late 1970s and the decade of 1980s showed that India was slow in modifying its industrial and trade-related policies in order to remain competent in the international arena. There was strong reliance on public sector initiatives, especially in the late 1960s, 1970s and beyond. The result was induction of insurmountable inefficiencies in basic operations and neglect in R&D operations and endeavor. As a consequence, 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 mechanism 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 towards an equitable distribution of wealth amongst its people. These policies did their best up to late 1980s but later started showing symptoms of weakening as the private sector became dominant over the public sector.

The salary structure of the employees which used to be quite remunerative in the public sector during 1960s and 1970s became less attractive than the salary structures in the successful Indian private sector and therefore the more talented

people started preferring private jobs. Moreover, multiple public sector technocrats left the public sector jobs and joined the private sector drug-manufacturing establishments, many of which were even set up by ex-public sector executives and employees. This started happening especially from mid 1970s. Indian pharmaceutical industry especially the public sector portion started showing symptoms of weakening the health-infrastructure-linked 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 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 its citizens should receive equitable opportunities in order 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 towards rationalization of equitable distribution of wealth.

Entrepreneurs create wealth. They are exceptionally intelligent people. They create wealth by deploying capital, labor and technology. Wealth created by them 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 towards 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 late 1980s. In the meantime, adoption of such policies bred the rise in corruption. Further, in pharmaceutical industry in particular, creation of industries with manufacturing capacities dispersed regionally without attention to economy of scale, 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 favourable for the public or local-industry to promote economic welfare could not last beyond the late1980s. 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, need arose to correct the situation. As a result, the Central Government modified the previous developmental policies from 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 in order 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 correct the situation gradually over a period of time. However, much more resources in a directed manner in mission-mode approach have to be diverted to enable India to emerge as a leader country to the development of novel APIs. Some frame work of activities and directions has been suggested in later parts.

Mastery on the Chemical reactions essential for generic APIs synthesis

It needs to be mentioned in this context that India has developed strong capabilities in

chemical synthesis 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, Clemensen reduction, cyanation and handling of inorganic cyanides, carboxylation, cryogenic reactions, enzymatic reaction, Dies-Alder condensation, Friedel-Craft alkylation and arylation, O-alkylation, N-alkylation, Grignard reaction, hazardous reaction (such as phosgenation, handling of carbon monoxide, inorganic cyanides) halogenation, Hofmann degradation, hydroboration and organoborane reactions, Meerwein-Pondorf-Valery reduction, Moffatt-Swern oxidation , organometallic reactions and many more including handling of hazardous reagents and sometimes working at very low temperatures. Indian capabilities exist for handling such reactions in pilot and industrial scale. 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 organised and it is growing at the rate of about 10per cent per annum in value terms.

Import-substitution research has limitations for development

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 strive to be a strong global player in 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 jack-pot drugs that have been successful in the international 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 jack-pot 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 1970s for certain time and this policy has promoted the country to reach the global heights in generic drugs 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 few hand-full of them, showing leadership by walking differently for novel invention. Those actors that walked to invent could not become successful in turning out any jack-pot category of new drugs. The main reason again was inadequate availability of resources. There are many other reasons too, which are not discussed here. It became clear that novel API discovery was not easy in India.

Novel drug discovery research: the main actors in India and the government support agencies

India is 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 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 falls short of, 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. 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. At present, in some institutions and in certain industry efforts have been intensified to discover novel APIs by using modern discovery techniques using computational techniques of utilizing advanced machine learning and analytical tools as also certain proprietary computational platforms for library design and synthesis of novel NCEs; utilisation of higher level chemistry techniques including multi-step synthesis, asymmetric synthesis, organometallic synthesis, stereospecific synthesis and complex hetereocyclic chemicals synthesis; and for novel biomolecular substances, use of synthetic techniques for the synthesis of nucleosides, glycolipids, phospholipids, phosphoramidites and peptides. However, such efforts are majorly in public–funded institutions, which have limited access to funds and are often not fully aware of the market needs. There is a stronger need for aligning such expertise with the industry and to jointly utilize such expertise for the development of novel APIs. Industry must be ready to invest large sums; myopic and advantage-deriving attitudes would not help. Forging stronger institute-industry tie ups, would require stronger protections of information, data, processes and technologies.

Actors of new drug discovery research in India need to concentrate on using phenotypic screening strategy, ligand-based drug designing and structure-based drug designing techniques. Strong multidisciplinary team needs to be created. Of late new drug discovery research is supported by the Government of India through programmes such as NMITLI, OSDD, SBIRI, BIPP, BIRAC, BIG, etc. Earlier initiated programs were TIFAC and TDB.

The NMITLI of CSIR was created to provide financial support to all players participating in the project. The financial support is in the form of grant-in-aid to the institutional partners in public domain; as soft loan with 3 per cent interest to the private sector industrial partners having more than 50 per cent of shareholding by Indians/ Non-resident Indians; and with 5 per cent interest to the private sector industrial partners having less than 50 per cent shareholding by Indians/ Non-resident Indians but with manufacturing base in India. As of 2020, no new drug (novel API) has yet come out from the NMITLI financial support. It was revealed in a recent analysis **[402]** that over one-third of funds distributed under an innovative public-private R&D initiative in the country might not come back to the public exchequer as the private firms that had taken these soft loans failed to produce tangible results. There has, therefore, to be better ways to fund novel drug discovery projects.

The translational research platform for drug discovery was created by the CSIR-UNIT: Open Source Drug Discovery (CSIR-OSDD), New Delhi in 2008 to facilitate the creation of collaborations among the experts in informatics, wet lab scientists, contract research organisations, clinicians, hospitals and others who are willing to adhere to the affordable healthcare philosophy. The consortium is extended to have people in the programme from foreign countries too. The vision of CSIR-OSDD is to achieve success to provide affordable healthcare by solving complex problems associated with discovering novel therapies for neglected tropical diseases

like Tuberculosis, Malaria and Leishmaniasis etc. A review of the project was undertaken by an independent group in 2012 to learn from the progress in order to understand how the multiple work plans move so as to generate more knowledge in understanding of how the concepts work in practice and how such projects be implemented. It was revealed that CSIR had committed to grant about INR 1.50 billion (US$35 million) and that about US$12 million were already paid for during the review period to various actors. Interestingly, most of the work was done by unpaid volunteers. Several peer–reviewed scientific papers came out of the project, which were significant. It was concluded that programme had enabled high quality research **[403]** at low cost. However, no new drug came out from the efforts.

In 2014 an independent assessment of the two grant programmes of the DBT namely the SBIRI and BIPP were carried out based on online surveys of 80 firms. It was concluded that that there is ample evidence that these two programmes were stimulating R&D as well as efforts to commercialise biotech products and services in the country. The Programmes were, therefore, considered to be successful **[404]** from these considerations. However, there was no evidence that these programmes had stimulated the conduct of R&D for the discovery/invention of novel APIs. Moreover, it is considered by the author that support to each individual programme in monetary term is considered inadequate to come out with novel APIs. Further, the team building of international caliber and the scope for inducting multidimensional actors in such programme is also inadequate. All these Government of India programmes are leaned towards supporting the SMEs and tiny business enterprises. Certainly these programmes have effectively and positively contributed towards strengthening the capabilities. The programmes have also contributed positively towards additional employment generation. However, massive infrastructure under one roof for the discovery of novel APIs seems to be missing from these programmes.

Assessment of Indian efforts in an independent study

In a survey carried out on the Indian companies between the period from 1994 and mid-2016 on proprietary drug discovery and development efforts **[405]**, mention was made of only one novel API coming from India. This was from Zydus Cadila Group (Cadila Healthcare), which was Saroglitizar, 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 was 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 study in February 2021, no other novel API matured from India.

Assessment of R&D progress in Indian Pharmaceutical Industry

In excellent studies carried out during the recent past **[406]**, it was argued that by introducing a set of policy reforms in the Indian pharmaceutical sector since mid-1990s and thereafter, the foreign MNCs as well as the Indian firms would invest in R&D for the development of new drugs besides developing cost-effective processes for generic APIs and novel formulations. While there was considerable increase in the deployment of resources in R&D since then by the Indian private sector companies, there was very small investment from foreign MNCs. Indeed, the foreign MNCs have intensified their efforts to sell their patented as well as the branded generic pharmaceutical formulations in India rather than investing on even manufacture of APIs in India. Over the years, the API manufacturing plants of the foreign MNCs in India have been sold out. Government of India from its various departments had also invested to promote R&D in pharmaceutical industry. However, all such

investments were almost exclusively diverted towards the development of cost-effective technologies for the manufacture of generic APIs, branded generic formulations and development of certain formulations for easing the delivery of active ingredients for increasing the efficacies of the medicines. It was further observed **[407-408]** that during the present time, even the generic API-producing industry has come under serious challenges and is facing steep market competition. Inventive policy supports are necessary to provide relief from such adversities. In the meantime, there is no published evidence to establish that India has entrenched leads in the manufacture of any novel API for introduction into the international market very soon. The author is of the opinion that for securing a leadership role in international context, the novel technological challenges, requiring the integration of multiple skills in the generic APIs manufacture as well as in novel API development would be the most important challenges in the future for remaining innovative, competitive and globally dominant. Efforts need to be made for this. Results can fructify only after many years of determined and systematic efforts.

R&D spending in major pharmaceutical industry companies

The total global expenditure on R&D spent by the pharmaceutical 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 per cent CAGR (2015-2022) **[409].** The top major global pharma companies listed on the basis of ranking of sales of their recently launched novel formulations in 2015, based on using their recently discovered novel APIs were Gileas Sciences,USA; Biogen, USA; Glaxo Smith Kline, UK;Roche., Switzerlang;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 a period of 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 Gileas Sciences,USA; Roche, Switzerland; Glaxo Smith Kline, UK; Novartis, Switzerland; Bristol-Myers Squibb, USA; Sanofi, France; Johnson& Johnson, USA; Merck&Co, USA; Pfizer,USA; and Astra Zenica,UK. The anticipated turnover of these ten 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. In order 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. It is true that the R&D spending of these companies is substantially high. For example , the R&D spend of top twenty 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 sending of pharma companies of US$149.8billion on R&D or about 59.8 per cent of the total. But spending of 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 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 stringent and greater demanding regulatory requirements for novel NCEs for approval as APIs; increasing costs of R&D, 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 novel chemical entity (NCE) takes about 4.5years, followed by preclinical testing of about one 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 overall probability of success for coming out with a novel API and its formulations in the market from start of a project to regulatory approval and marketing is about 4.1 per cent only, with break ups of 51 per cent up to discovery of an active NCE; about 69 per cent from active NCE to up to reaching pre-clinical stage; about 12.8 per cent from multiple phase trials; and about 91 per cent during the submission phase **[410]**. It is reported **[411]** in another study that the overall success is about 4.9 per cent. This study had analyzed one hundred numbers of US FDA authorized novel APIs, approved during the period 2006 to 2014 for 13 numbers of 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); Astra Zeneca, U K(7); Novratis, Switzerland 13); Amgen,USA(6); GSK,UK(12); Takeda, Japan(6);Bristol-Meyer 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 to 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 taking innovative changes in their R& D policy approach and design to improve upon their overall efficiency. It is also to be taken note of 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, which contributes to increased costs.

In another study **[412]** , 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 was US$2.870 billion. The 2020 costs are projected by the author to US$ 3.169 billion, taking into consideration the annual inflation rate during the period 2013-2020.

In yet another recent study **[413]** 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 per cent of the total approved new drugs), which were developed by 47 different companies.

Estimated expenditure-needs in India for novel API development and fund raising avenues

Indian policy makers and researchers would have to take the above success rates into account, analyze each stage of drug development in its nitty-gritty, and find the gap areas for improvement with a view to improve upon the overall success rate. India can also evolve its own strategy and plan for the future. The huge costs contemplated should not frighten as innovative methods and policies can be evolved to find the required amounts. Since the latest estimate for developing a novel API and its formulations have 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 work out to US$ 95.43 million or about INR 668.42 crores per year per novel API. This figure can be used as the base line figure to calculate the fund deployment. Assuming that India would plan to come out with 10 novel APIs over a period of 14 years, the monetary deployment would be about INR 6684.2crores 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. It is likely that multiple benefits may start accruing much before the target period.

India has presently 1.46 crore tax payer **[414]** and that in the Indian budget 2020, the gross tax revenue was pegged at INR 24,23,020 crore. 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 **[415]** reached INR 1.4 lakh crore (US$ 20.03 billion) in 2019, up 9.8 per cent from Rs 129,015 crore (US$ 18.12 billion) in 2018. Pharmaceuticals export stood at US$ 20.70 billion in FY20. The turnover of Indian pharmaceutical sector is expected to grow to US$ 100 billion by 2025.

Indian government can raise the calculated monetary amount of INR 6684.2 crore per year from the above infrastructure in order to build an innovative novel API discovering infrastructure. India also has a pool of very ordinary farmers over 8.5 crore in numbers who have Bank Accounts for receiving an income support from PM Kisan **[416]** program, which is a Central Government scheme. This huge pool of man power 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 INR120.00 per year per individual farmer; the total sum that can come from this source can be INR1020 crore, 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 has 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 jack-pot discoveries.

Suggestions for moving forward for novel API discovery in India

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 & Fertilizers, Department of Pharmaceuticals or the Ministry of Science &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 & Technology Minister/ Prime Minister. The enterprise shall work on policy level as well as would have 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 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 of 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 multi-directional 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) out-sourcing of services linked with drug discovery that are available at cheaper prices and do 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/ organisation attached with renowned hospitals etc, (d) expert consultancy organisations that can assist in identifying expertise available in elsewhere in clinical trials, regulatory affairs, safety solving issues, quality management issues, hiring of c GMP facilities for the manufacture of substances for clinical trial etc.

On 25 September 2014, the Indian government announced **[417]** 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 quantum increase in multiple areas of the manufacturing sector's annual growth rate so as 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 per cent by 2025 from the present 16 per cent. The Drugs and Pharmaceuticals Industry is also within the ambit of the manufacturing sector. The pharmaceutical industry which is highly technology dependant 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 the 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 in 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 man-power and because of Indian's skills in chemistry and engineering sciences besides the availability of multiple number of capital goods and materials including auxiliary materials at more competitive prices. In addition, there have been enormous efforts from time to time through both Industrial as well as 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 the Indian SMEs. However, these measures fell short of for 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 remuneration-earning area such as the sales jobs in enterprises, banking and accounting

jobs, powerful administrative jobs and many others where 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. Invention in new APIs holds the potentials of generating cutting-edge wealth for countries as these would not only 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.

Amazingly, while presenting the Indian budget in the Parliament, the Finance Minister Nirmala Sitharaman announced **[418]** to have earmarked INR 50,000 crore (US$ 7.143 billion) over five years for the creation of a National Research Foundation (NRF) , which shall be an umbrella body that is expected to fund research across a range of disciplines, from science and technology to humanities. The creation of the NRF is an achievement of great futuristic vision. Development of novel APIs need to be an important discipline and task, which can be a part of the NRF.

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. 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 effect a treatment; and the technologists venture to develop cost-effective manufacturing processes to provide these for use by the diseased individuals. The regulators decide on authorisation for use of novel products. The policy makers 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 these framework, 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 framed 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 produce 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 action plan, start implementation with periodic reviews and make progress. 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.

The environment has to be most competitive with ready rewards for the achievers and provisions for firing incompetence. Enough time is required to be extended for the executers of research in multiple facets of inputs that determine success. Reward system based on influential and powerful individual assessment is dangerous for a grand teamwork to succeed.

Annexure

Table 3: Major Generic APIs Manufactured in India and Exported

NAMES OF THE APIs	THERAPEUTIC CLASS/USE
1. ABACAVIR/SULFATE/HCL	Antiretroviral drug to treat HIV/AIDS.
2. ABIRATERONE ACETATE	A kind of hormone therapy classified as an adrenal inhibitor
3. ACAMPROSATE CALCIUM	To treat alcohol dependence
4. ACENOCOUMAROL	Anticoagulant
5. ACETAZOLAMIDE	Belongs to diuretic and carbonic anhydrase inhibitors , used to treat glaucoma, epilepsy etc
6. ACITRETIN	Oral retinoid (vitamin-A derivative) used to treat severe psoriasis
7. ACYOLOVIR	Antiviral medication to treat herpes simplex , chickenpox, shingles etc
8. ADAPALENE	Treatment of mild-moderate acne, keratosis pilaris and other skin conditions
9. ADENOSINE	Used for conversion to sinus rhythm of paroxysmal supraventricular tachycardia
10. ADEFOVIR DIPIVOXIL	Antiviral drug to treat hepatitis B infection
11. AGRATROBAN	Anticoagulant
12. ALBUTEROL SULFATE/ SALBUTAMOL SULFATE	A short-acting β2 adrenergic receptor agonist used to treat asthma &COPD
13. ALENDRONATE SODIUM/ SODIUM TRIHYDRATE	Prevention & treatment of osteoporosis
14. ALFUSOLINE HCL	Treatment of benign prostatic hyperplasia
15. ALLOPURINOL	To treat gout
16. ALOGLIPTIN BENZOATE	Antidiabetic drug
17. ALPHACALCIDOL	Supplementation of vitamin D-3
18. ALPRAZOLAM	Anxiolytic drug ,to treat short-term management of anxiety disorders specifically panic disorder or generalized anxiety disorder
19. AMBROXOL HYDROCHLORIDE	To treat respiratory diseases with high mucus
20. AMIFOSTINE	Used in cancer patients to reduce the incidence of neutropenia-related fever and infection induced by DNA-binding chemotherapeutic agents
21. AMIODARONE HCL	Cardiovascular drug to treat serious, life-threatening ventricular arrhythmias
22. AMILORIDE BESYLATE/ MESYLATE MONOHYDRATE	Cardiovascular drug against high BP
23. AMISULPRIDE	Antiemetic and antipsychotic medication to prevent and treat postoperative nausea and vomiting

Table 3 continued...

Table 3 continued...

24. AMITRIPTYLINE HYDROCHLORIDE	Antidepressant to induce sleep
25. AMLODIPINE BESYLATE	Cardiovascular drug against high BP
26. AMOXAPINE	Antidepressant drug
27. AMPHOTERICIN -B	Antifungal antibiotic
28. ANAGRELIDE	To treat essential thrombocytosis
29. ANASTROZOLE	Medication to treat breast cancer
30. ANIDULAFUNGIN	Antifungal semi-synthetic antibiotic
31. APIXABAN	Cardiovascular drug-anticoagulant
32. APREPITANT	To prevent chemotherapy-induced nausea and vomiting
33. ARFORMOTEROL TARTRATE	To treat chronic obstructive pulmonary disease
34. ARIPIPRAZOLE	Antipsychotic drug used to treat bipolar disorder, schizophrenia, Tourette's syndrome etc
35. ARMODAFINIL	To treat excessive sleepiness caused by sleep apnea, narcolepsy, or shift work sleep disorder
36. APREPITANT	To prevent chemotherapy-induced nausea and vomiting
37. ARTEETHER	Antimalarial drug
38. ARTEMETHER	Antimalarial drug
39. ARTESUNATE	Antimalarial drug
40. ATAZANAVIR SULFATE	Antiretroviral drug to treat HIV
41. ATENOLOL	Cardiovascular drug beta blocker to treat high BP
42. ATOMOXETINE HCL	To treat attention deficit hyperactivity disorder
43. ATORVASTATIN CALCIUM / CALCIUM TRIHYDRATE/ MAGNESIUM/ AMORPHOUS& CRYSTALLINE	Cardiovascular hyperlipidimic drug
44. ATOVAQUONE	To treatment of Pneumocystis jevorici (formerly carinii) pneumonia. P.jevorici is a yeast-like fungus.
45. ATROPINE SUPHATE / SUPHATE HYDRATE	Used to treat low heart rate, reduce salivation and bronchial secretions before surgery, also as an antidote for overdose of cholinergic drugs or poisoning
46. AVANAFIL	Used as therapy of erectile dysfunction
47. AXITINIB	Anticancer drug
48. AZACITIDINE	Chemotherapeutic agent for cancer treatment
49. AZATHIOPRINE	Antiarthritic drug to treat rheumatoid arthritis
50. AZILSARTAN MEDOXOMIL POTASSIUM	Cardiovascular drug ,angiotensin receptor blocker, to treat high BP
51. AZITHROMYCIN MONOHYDRATE/DIHYDRATE	Antibiotic, macrolide

Table 3 continued...

Table 3 continued...

52. BACLOFEN / R (+) BACLOFEN	Muscle relaxer and antispasmodic agent
53. BECLOMETHASONE DIPROPIONATE	Steroid medication used to treat asthma, various dermatitis and psoriasis, ulcerative colitis , allergic rhinitis , nasal polyps etc
54. BENAZEPRIL HCL	Cardiovascular drug against high BP
55. BENDAMUSTINE HCL MONOHYDRATE	Chemotherapy for multiple cancers
56. BENDROFLUMETHIAZIDE	Cardiovascular drug against high BP
57. BENZARONE	Uricosuric agent used to treat gout
58. BENZBROMARONE	Uricosuric agent used to treat gout
59. BENZETHONIUM CHLORIDE	To treat minor cuts, scrapes, wounds, or cracked skin
60. BENZOYLPEROXIDEHYDROUS	Mostly used to treat acne, either alone or in combination with other treatments
61. BENZYDAMINE HYDROCHLORIDE	Analgesic, anti-inflammatory drug
62. BETAHISTINE DIHYDROCHLORIDE	Ménière's disease and vertigo
63. BETAMETHASONE/ DIPROPIONATE/VALERATE/ SODIUM PHOSPHATE	Steroid medication, used to treat rheumatic disorders , skin diseases , allergic conditions such as asthma , Crohn's disease, cancers etc.
64. BETAXOLOL HCL	A selective beta receptor blocker used in the treatment of hypertension and glaucoma
65. BETHANECHOL CHLORIDE	To treat the symptoms of Urinary Retention
66. BEXAROTENE	Anti-cancer drug
67. BICALUTAMIDE	Antiandrogen medication to treat prostate cancer
68. BIMATOPROST	Anti-glaucoma drug
69. BIPERIDEN/ HCL	Anti-Parkinson disease drug
70. BISOPROLOL FUMARATE	Cardiovascular drug against high BP
71. BIVALIRUDIN	A synthetic peptide,a potent and highly specific inhibitor of thrombin, used as an anticoagulant
72. BORTEZOMIB	Chemotherapy for multiple cancers
73. BOSENTAN MONOHYDRATE	Cardiovascular drug to treat pulmonary hypertension
74. BREXPIPRAZOLE	Antipsychotic drug used to treat schizophrenia and major depressive disorders
75. BRIMONIDINE TARTRATE	Treatment of glaucoma
76. BRINZOLAMIDE	Treatment of glaucoma
77. BRIVARACETAM	Anticonvulsant
78. BROMAZEPAM	Anxiolytic drug and hypnotic medication
79. BROMXEDINE HCL	Expectorant or a mucolytic drug used to treat of respiratory disorders
80. BROMFENAC SODIUM	Nonsteroidal anti-inflammatory drug

Table 3 continued...

Table 3 continued...

81. BROTIZOLAM	Sedative and hypnotic drug
82. BUCLIZINE HCL	Antihistaminic drug
83. BUDESONIDE	To treat certain bowel conditions such as Crohn's disease, ulcerative colitis
84. BUPROPION HYDROCHLORIDE	Antidepressant
85. BUSPIRONE HCL	Anxiolytic drug, to treat anxiety disorders
86. BUSULFAN	Chemotherapy for multiple cancers
87. CABAZITAXEL	Anticancer drug for multiple cancers
88. CALCIPOTRIOL MONOHYDRATE(also known as CALCIPOTRIENE)	Supplement of Vitamin- D
89. CALCITRIOL	Supplement of Vitamin- D
90. CALCIUM LEVULINATE	Use d for calcium nutrition
91. CALCIUM POLYSTYRENE SULPHONATE	Used as a potassium binder in acute and chronic kidney disease in hyperkalemia
92. CAMYLOFIN DIHYDROCHLORIDE	Anti-spasmodic medication
93. CANDESARTAN CILEXETIL	Cardiovascular drug ,angiotensin receptor blocker used to treat high BP
94. CAPECITABINE	Chemotherapy for breast cancer
95. CARBAMAZEPINE	Anticonvulsant to treat epilepsy and neuropathic pain
96. CARBOPLATIN	Chemotherapy for multiple cancers
97. CARFILZOMIB	Anti-cancer medication
98. CARISOPRODOL	To treat musculoskeletal pain
99. CARMUSTINE	Cancer chemothrapy
100. CARPROFEN	Nonsteroidal anti-inflammatory drug
101. CARVEDILOL / PHOSPHATE	Cardiovascular drug , to treat high BP
102. CEFDINIR	Antibiotic ,used to treat a number of bacterial infections
103. CEFIXIME	Antibiotic , used to treat a number of bacterial infections
104. CELECOXIB	Non-steroidal anti-inflammatory drug
105. CETRIMIDE	Antiseptic and disinfectant
106. CETRIZINE HCL/ DIHYDROCHLORIDE	Antihistaminic drug
107. CHLORAMPHENICOL/ PALMITATE	Broad spectrum antibiotic
108. CHLORDIAZEPOXIDE	Anxiolytic drug
109. CHLORHEXIDINE BASE/ GLUCONATE/DIACETATE/ DIHYDROCHLORIDE	Disinfectant and antiseptic drug

Table 3 continued...

Table 3 continued...

110. CHLOROBUTANOL HEMIHYDRATE	Sedative and hypnotic drug
111. CHLOROPYRAMINE	Antihistaminic drug
112. CHLOROQUIN PHOSPHATE	Antimalarial drug
113. CHLOROTHIAZIDE	Diuretic drug
114. CHLORPHENESIN / CARBAMATE	Muscle relaxant, used to treat muscle pain
115. CHLORPROMAZINE HYDROCHLORIDE	Antipsychotic drug used to treat psychotic disorders
116. CHLORTHALIDONE	Cardiovascular drug against high BP
117. CHOLINE FENOFIBRATE	A lipid-lowering agent used to treat severe hypertriglyceridemia, primary hyperlipidemia, and mixed dyslipidemia
118. CILAZAPRIL	Cardiovascular drug ,an ACE inhibitor, used to treat high BP
119. CIMETROPIUM BROMIDE	Antimuscarinic drug, a semi-synthetic belladonna alkaliod, used for long-term treatment of irritable bowel syndrome
120. CINACALCET HCL	To treat secondary hyperparathyroidism
121. CINNARIZINE	An antihistamine & a calcium channel blocker used to treat nausea and vomiting
122. CISPLATIN	Cancer chemotherapy medication
123. CITALOPRAM HBR/ HCL	Antidepressant to treat major depressive disorder, obsessive compulsive disorder, panic disorder and social phobia
124. CLARITHROMYCIN	Antibiotic, macrolide
125. CLOBAZAM	Anticonvulsant and anxiolytic drug
126. CLOBETASOL PROPIONATE	Corticosteroid to treat skin conditions such as eczema, contact dermatitis, seborrheic dermatitis, and psoriasis.
127. CLOBETASONE BUTYRATE	Steroid drug used to treat eczema, contact dermatitis, psoriasis, insect bites and stings, nappy rash etc
128. CLOFARABINE	Anticancer drug, To treat relapsed or refractory acute lymphoblastic leukaemia
129. CLONAZEPAM	Anticonvulsant drug
130. CLOMIPRAMINE HCL	Antidepressant
131. CLOPIDOGREL HYDROGEN SULFATE/BISULFATE	To prevent atherothrombotic events
132. CLOSANTEL/SODIUM	Veterinary, anti-parasitic drug
133. CLORSULON	Veterinary drug to treat liver fluke
134. CLOTIAZEPAM	Anxiolytic drug
135. CLOZAPINE	Antipsychotic medication to treat schizophrenia
136. CHLORTHALIDONE	Cardiovascular drug to treat high BP

Table 3 continued...

Table 3 continued...

137. CHLORZOXAZONE	Muscle relaxant
138. CHOLESTYRAMINE RESIN	To reduce blood choleterol
139. CICLESONIDE	Nonhalogenated, synthetic, inhaled corticosteroid with anti-inflammatory and potential antiviral activities
140. CIDOFOVIR	Antiviral drug to treat cytomegalovirus retinitis in people with AIDS
141. CILAZAPRIL	Cardiovascular anti ACE drug to treat high BP
142. CILNIDIPINE	Cardiovascular drug, Calcium channel blocker, to treat high BP
143. CILOSTAZOL	Cardiovascular drug -vesodilator
144. CIS PLATIN	Chemotherapy to treat many cancers
145. CITALOPRAM HBR	Antidepressant to treat depression
146. CLARITHROMYCIN	Antibiotic
147. CLENBUTEROL HYDROCHLORIDE	A steroid-like substance used for weight loss and body building. Banned in many countries.
148. CLIDINIUM BROMIDE	Anticholinergic agent
149. CLOFARABINE	Anticancer drug to treat acute lymphoblastic leukaemia
150. CLOMIPHENE CITRATE	Used to treat infertility in women
151. CLONIDINE/CLONIDINE HCL	Cardiovascular to treat high BP
152. CLOPIDOGREL BISULPHATE	Cardiovascular antiplatelet medication
153. CLOPROSTENOL SODIUM -DL	A luteolytic agent, causing corpus luteum to stop production of progesterone, and to reduce in size over several days , which induce estrus and to cause abortion. Used in animals
154. CLORSULON	Veterinary anti-parasitic drug , used to treat adult liver flukes in cattle
155. CLOSANTEL SODIUM	Anti parasitic drug
156. CLOTRIMAZOLE	Antifungal drug
157. COLCHICINE	To treat inflammation and painm in gout
158. COLESEVELAM HCL	Bile acid sequestrant to reduce LDL-Cholesterol
159. COLISTIMETHATE SODIUM [also known as COLISTIN]	Broad-spectrum polymyxin antibiotic, used against most aerobic Gram-negative bacteria except Proteus bacteria
160. CRIZOTINIB	Anticancer drug to treat non-small cell lung carcinoma
161. CYCLOBENZAPRINE HCL	Muscle relaxant
162. CYCLOPENTOLATE HYDROCHLORIDE	To dilate the eye for eye examinations
163. CYCLOPHOSPHAMIDE/ MONOHYDRATE	Chemotherapy to treat many cancers
164. CYCLOSERINE	Anti TB drug
165. CYCLOSPORINE	Immunosuppressant drug

Table 3 continued...

Table 3 continued...

166. CYPROHEPTADINE HYDROCHLORIDE	Antihistaminic drug , used to treat hypersensitivity reaction
167. DABIGATRAN ETEXILATE MESYLATE	Cardiovascular drug used as an anticoagulant
168. DACLATASVIR DI HCL	Antiviral drug to treat hepatitis C
169. DACTINOMYCIN (Also called ACTINOMYCIN-D)	Anticancer drug
170. DAPAGLIFLOZINE PROPANEDIOL MONOHYDRATE	Antidiabetic drug
171. DAPOXETINE HYDROCHLORIDE	To treat men with premature ejaculation
172. DAPSONE	Anti-leprosy drug, antifungal and anti acne medication
173. DARIFENACIN HBR	A medication used to treat urinary incontinence
174. DARUNAVIR AMPRPHOUS / ETHANOLATE/n-PROPIONATE	Antiretroviral drug to treat HIV/AIDS
175. DASATINIB	An oral iron chelator used to reduce chronic iron overload
176. DECITABINE MONOHYDRATE	Anticancer drug to treat blood cell dysfunction
177. DEFERASIROX	An oral iron cheater used to reduce chronic iron overload
178. DECITABINE	Cancer chemotherapy drug to treat myelodysplastic syndromes
179. DEFERASIROX	Iron chelator for reducing iron overload
180. DEFLAZACORT	Steroid drug used as an anti-inflammatory and immunosuppressant drug
181. DELAFLOXACIN	Fluoroquinolone antibiotic
182. DESLORATADINE	Antihistamine to treat allergies
183. DESMOPRESSIN ACETATE	To treat diabetes insipidus, bedwetting, hemophilia A, von Willebrand disease, and high blood urea levels. An antidiuretic peptide drug
184. DESONIDE	To treat a variety of skin conditions like eczema, dermatitis, allergies and rash
185. DESOXIMETASONE	Steroid drug used in dermatoses, skin allergies, psoriasis etc
186. DESVENLAFAXINE SUCCINATE	Antidepressant
187. DEXAMETHASONE SODIUM PHOSPHATE	Steroid hormone used to treat rheumatic problems, a number of skin diseases, severe allergies, asthma, chronic obstructive lung disease etc
188. DEXKETOPROFEN TROMETAMOL	Non-steroidal anti-inflammatory drug
189. DEXLASOPRAZOLE	Anti-ulcerant drug
190. DEXMEDETOMIDINE HCL	Analgesic, anxiolytic and sedative

Table 3 continued...

Table 3 continued...

191. DEXMETHYLPHENIDATE HCL	To treat attention deficit hyperactivity disorder over the age of five years
192. DEXTROMETHORPHAN HYDROBROMIDE	Antitussive drug ,cough suppressant with sedative, dissociative, and stimulant properties
193. DIACEREIN	To treat joint diseases such as osteoarthritis
194. DICLOFENAC ACID/SODIUM/ POTASSIUM/DIETHYLAMINE	Nonsteroidal anti-inflammatory drug
195. DIAZEPAM	Anxiolytic drug
196. DIOSMIN	Dietary supplement to aid treatment of hemorrhoids of legs
197. DICYCLOMINE HCL(also known as DICYCLOVERINE HCL)	To treat spasms of the intestines such as occur in irritable bowel syndrome
198. DIDANOSINE	Antiretroviral therapy to treat HIV
199. DIFLUNISAL	To treat chronic arthritis and acute pain
200. DIGOXIN	To treat heart failure
201. DILOXANIDE FUROATE	To eradicate cysts of E. histolytica in asymptomatic carriers
202. DILTIAZEM HYDROCHLORIDE	Calcium channel blocker used to treat high BP, angina, and certain heart arrhythmias
203. DIMETHICONE	A silicone-based polymer,used in topical creams and ointments. Aso used as an anti-foaming agent, a hair and skin conditioner, and in the treatment of head lice and, as an anti-bloating/anti-flatulence agent .
204. DIMETHYL FUMERATE	An oral therapy for psoriasis ;has been approved as a treatment option for adults with relapsing multiple sclerosis
205. DIMINAZENE DIACETURATE	An antiparasitic agent
206. DIOSMIN	A flavone glycoside of diosmetin ,used as a non-prescription dietary supplement to aid treatment of hemorrhoids or chronic venous diseases, mainly of the legs
207. DIPHENHYDRAMINE HYDROCHLORIDE/CITRATE	An antihistamine drug to treat allergies
208. DIROXIMEL FUMERATE	Approved for the treatment of relapsing forms of multiple sclerosis
209. DIVALPROEX SODIUM	To treat manic episodes associated with bipolar disorder, epilepsy, and migraine headaches
210. DOBUTAMINE HYDROCHLORIDE	Cardiovascular drug used to treat cardiogenic shock and severe heart failure
211. DOCETAXEL TRIHYDRATE	Broad spectra antineoplastic drug
212. DOFETILIDE	Cardiovascular drug used for maintenance of sinus rhythm in individuals prone to the occurrence of atrial fibrillation

Table 3 continued...

Table 3 continued...

213. DOLASETRON MESYLATE	Antinauseant and antiemetic agent
214. DOLUTEGRAVIR SODIUM	Antiretroviral drug to treat HIV-I
215. DOMPERIDONE MALEATE	Antiemetic, gastric prokinetic agent
216. DONEPEZIL HCL	To treat Alzheimer's disease
217. DORZOLAMIDE HYDROCHLORIDE	To treat occular pressure including glaucoma
218. DOTHIEPIN HCL also called as DOSULEPIN HCL	Antidepressant
219. DOXAZOSIN MESYLATE	To treat high BP and symptoms of benign prostatic hyperplasia
220. DOXOFYLLINE	Antiasthmatic drug
221. DOXORUBICIN HCL	Cancer chemotherapy drug to treat breast cancer, bladder cancer, Kaposi's sarcoma, lymphoma, and acute lymphocytic leukemia
222. DOXYLAMINE SUCCINATE	Antihistaminic drug, used to treat allergy, common cold etc
223. D-PENICILLAMINE	Chelating agent to treat heavy metal poisoning
224. DRONEDARONE HCL	Cardiovascular drug used in cardiac arrhythmias
225. DROTAVERINE HCL	Antispasmodic drug, used to enhance cervical dilation during childbirth
226. DROXIDOPA	Anti-Parkinson drug
227. DULOXETINE HYDROCHLORIDE	Antidepressant to treat major depressive disorder, generalized anxiety disorder, fibromyalgia, and neuropathic pain
228. DUTASTERIDE	To treat enlarged prostate ailments
229. ECONAZOLE NITRATE	Broad-spectrum antifungal drug
230. EFAVIRENZ	Antiretroviral drug to treat HIV
231. ELETRIPTAN HBR	Treatment of migraine & headaches
232. ELTROMBOPAG	Immune thrombocytopenic purpura drug to increase the number of platelets
233. EMPAGLIFLOZIN	Antidiabetic drug
234. EMTRICITABINE	Antiviral drug to treat HIV
235. ENTACAPONE	To treat Parkinson's disease
236. ENZALUTAMIDE	Anticancer drug to treat prostate cancer
237. EPERISONE HYDROCHLORIDE	Skeletal muscles relaxant
238. EPLERENONE	A potassium-sparing diuretic
239. EPROSARTAN MESYLATE	Cardiovascular drug, angiotensin II antagonist , used to treat high BP
240. ERIOTINIB/ HCL	Anticancer drug to treat bronchioloalveolar carcinoma

Table 3 continued...

Table 3 continued...

241. ERYTHROMYCIN/ ESTOLATE/ ETHYL SUCCINATE/ PHOSPHATE/STEARATE	Antibiotic, macrolide
242. ESCITALOPRAM OXALATE	Antidepressant
243. ESLICARBAZEPINE ACETATE	Anticonvulsant drug
244. ESOMEPRAZOLE MAGNESIUM DIHYDRATE/ TRIHYDRATESODIUM	To treat gastroesophageal reflux disease, like proton pump inhibitors
245. ESTAZOLAM	Hypnotic and sedative drug
246. ESZOPICLONE	Sedative-hypnotics, to treat sleeping disorder
247. ETRAVIRINE	Antiretroviral drug to treat HIV
248. ETHACRYNIC ACID	To treat edema caused by medical problems
249. ETHAMBUTOL HCL	Anti-tuberculosis drug
250. ETHAMSYLATE	
251. ETIZOLAM	Anxiolytic drug
252. ETODOLAC	Non-steroidal anti-inflammatory drug
253. ETOPOSIDE	Chemotherapy to treat many cancers
254. ETORICOXIB	Non-steroidal anti-inflammatory drug, to treat arthritis
255. ESZOPICLONE	Treatment of insomnia
256. EVEROLIMUS	Immunosuppressant drug
257. EZETIMIBE	Cholesterol absorption inhibitor with lipid-lowering activity
258. FAMOTIDINE	Histamine H2 receptor antagonist -antacid
259. FAMPRIDINE(also known as DALFAMPRIDINE and 4-AMINOPYRIDINE)	Used to manage symptoms of multiple sclerosis
260. FEBANTEL	Antiparasitic drug of dogs
261. FEBUXOSTAT	Antigout medicine
262. FELBINAC	Nonsteroidal anti-inflammatory drug
263. FELODIPINE	Cardiovascular drug to treat high BP
264. FENASTERIDE	Benign prostatic hyperplasia therapy
265. FENBENDAZOLE	Broad spectrum anthelmintic used to treat gastrointestinal parasites
266. FENOFIBRATE	Cardiovascular -to treat abnormal blood lipid levels
267. FENOFIBRIC ACID /CHOLINE SALT	Cardiovascular lipid-lowering agent
268. FENOPROFEN CALCIUM	Non-steroidal anti-inflammatory drug
269. FESOTERODINE FUMERATE	Antimuscarinic drug to treat overactive bladder syndrome
270. FEXOFENADINE HYDROCHLORIDE	Antihistaminic drug

Table 3 continued...

Table 3 continued...

271. FIDAXOMICIN	Antibiotic macrolytic
272. FINASTERIDE	To treat benign prostatic hyperplasia in men
273. FINGOLIMOD HCL	An immune-suppressive drug
274. FLAVOXATE HCL	To treat certain bladder/urinary tract symptoms
275. FLECAINIDE ACETATE	Cardiovascular drug to treat anti-arrhythmia & tachyarrhythmia
276. FLIBANSERIN	To treat pre-menopausal women with hypoactive sexual desire disorder
277. FLUCONAZOLE	Antifungal medication
278. FLUTAMIDE	Non-steroidal anti-androgen drug to treat prostate cancer
279. FLUTICASONE PROPIONATE	Antiallergic, antiinflammatory and antipruritic drug
280. FLUCONAZOLE	Antifungal drug
281. FLUFIBROFEN	Nonsteroidal anti-inflammatory drug
282. FLUNARIZINE DI HCL	A selective calcium entry blocker used to treat migraine, occlusive peripheral vascular disease, vertigo and epilepsy
283. FLUOCINOLONE ACETONIDE	Corticosteroid used in dermatology
284. FLUOXETINE HYDROCHLORIDE	Antidepressant
285. FLUPHENAZINE DECANOATE	Anti-psychotic drug
286. FLUPEVTIXOL DIHYDROCHLORIDE	Antipsychotic drug
287. FLURBEPROFEN / SODIUM	Nonsteroidal anti-inflammatory drugs
288. FLUTICASONE PROPIONATE	Corticosteroid
289. FLUVASTATIN SODIUM	Cardiovascular lipid-lowering agent
290. FLUVOXAMINE MALEATE	Antidepressant
291. FONDAPARINUX SODIUM	Anticoagulant medication
292. FOSAPREPITANT DIMEGLUMINE	Antiemetic medication
293. FOSCARNET SODIUM	Antiviral drug to treat cytomegalovirus retinitis in HIV
294. FOSINOPRIL SODIUM	Cardiovascular anti ACE drug to treat high BP
295. FROVATRIPTAN SUCCINATE	To treat vascular headaches and migraine
296. FULVESTRANT	To treat hormone receptor (HR)-positive metastatic breast cancer in postmenopausal women
297. FUROSEMIDE	Diuretic drug
298. GABAPENTIN	Anticonvulsant to prevent and control seizures
299. GADOPENTETIC ACID	MRI contrast agent
300. GALANTAMINE HBR	Alzheimer's disease treatment
301. GANIRELIX / ACETATE	A competitive gonadotropin-releasing hormone antagonist used in assisted re production to control ovulation

Table 3 continued...

Table 3 continued...

302. GATIFLOXACIN / HEMIHYDRATE	Antibacterial drug -fluoroquinolone family-banned in India
303. GEFITINIB	Anticancer drug , EGFR inhibitor, to teat cancer of breast , lungs etc
304. GEMCITABINE HCL	Chemotherapy to treat many cancer
305. GLIBENCLAMIDE /GLYBURIDE	Antidiabetic drug
306. GLICLAZIDE	Anti-diabetic drug
307. GLIMEPIRIDE	Antidiabetic drug
308. GLIPIZIDE	Antidiabetic drug
309. GLYBURIDE	Antidiabetic drug
310. GLYCOPYRROLATE/ GLYCOPYRRONIUM BROMIDE/ TOSYLATE	To treat excessive underarm sweating. Aso used to reduce salivary, tracheobronchial, and pharyngeal secretions
311. GRANISETRON HCL/BASE	Antiemetic to treat nausea
312. GUAIFENESIN/ HCL	Expectorant
313. HALOBETASOL PROPIONATE	Synthetic corticosteroid with anti-inflammatory, antipruritic, and vasoconstrictor activities
314. HALOPERIDOL/ DECONATE	Sedative
315. HOMATROPINE METHYLBROMIDE	Anticholinergic drug
316. HYDRALAZINE HCL	Antihypertensive drug
317. HYDROCHLOROTHIAZIDE	Diuretic drug
318. HYDROCORTISONE	Synthetic glucocorticoid drug used for anti-inflammatory and to treat allergic conditions
319. HYDROXYCHLOROQUINE SULPHATE	Anti-malarial drug
320. HYOSCINE / BUTYLBROMIDE / HYDROBROMIDE	To treat crampy abdominal pain, oesophageal spasms, renal colic, and bladder spasm
321. HYOSCYAMINE HBR / SULPHATE	Anticholinergic drug
322. IBANDRONATE SODIUM MONOHYDRATE/IBANDRONIC ACID MONOSODIUM MONOHYDRATE	To treat osteoporosis and metastasis-associated skeletal fractures in cancer
323. IBRUTINIB	Anticancer drug
324. IBUPROFEN	Non-steroidal anti-inflammatory drug
325. IFOSFAMIDE	Anticancer drug to treat multiple types of cancer
326. IMATINIB MESYLATE /ALPHA	Chemotherapy to treat cancer
327. IMATINIB MESYLATE BETA	Chemotherapy to treat cancer

Table 3 continued...

Table 3 continued...

328. IMIPRAMINE HCL/PAMOATE	Antidepressant to treat depression
329. IMIQUIMOD	To treat actinic keratoses
330. INNOTECAN HCL	Anticancer drug to treat cancer of colon and rectum
331. IOPROMIDE	Non-ionic X-ray contrast agent for intravascular administration
332. IPRATROPIUM BROMIDE	To treat chronic obstructive pulmonary disease and asthma
333. IRBESARTAN	Cardiovascular drug ,anti ACE-II inhibitor to treat high BP
334. IRINOTECAN HCL TRIHYDRATE	Chemotherapy for colon cancer
335. IRON SUCROSE COMPLEX / IRON SACCHARATE	To treat iron deficiency anemia with chronic kidney disease
336. ISOMETAMEDIUM CHLORIDE HCL	Veterinary medicine used as a trypanocidal
337. ISOTRETINOIN	Anti-cancer drug to treat severe acne, neuroblastoma in children, cutaneous T-cell lymphomas and squamous cell skin cancers
338. ISRADIPINE	Cardiovascular drug, a calcium channel blocker, used to treatb high B P
339. ITOPRIDE HCL	Used for treatment of functional dyspepsia and other gastrointestinal conditions
340. ITRACONAZOLE	Antifungal medication
341. IVABRADINE ADIPATE/ HCL	Cardiovascular drug to treat stable heart-related chest pain
342. IVACAFTOR	To treat cystic fibrosis. Cystic fibrosis are genetic defects related to cancer.
343. IVERMECTIN	Anti-parasitic drug
344. KETOCONAZOLE	Antifungal drug
345. KETOPROFEN	Nonsteroidal anti-inflammatory drug
346. KETOROLAC TROMETHAMINE	Non-steroidal anti-inflammatory drug
347. LACIDIPINE	Cardiovascular-Calcium channel blocker
348. LACOSAMIDE	To treat partial-onset seizures and diabetic neuropathic pain.
349. LAMIVUDINE	Antiretroviral drug used to treat HIV
350. LAMOTRIGENE	Anticonvulsant drug to treat epilepsy &bipolar disorder
351. LANTHANUM CARBONATE	Used as a phosphate binder in chronic kidney disease
352. LANSOPRAZOLE	Proton pump inhibitors
353. LAPATINIB DITOSYLATE MONOHYDRATE	Anticancer drug to treat solid tumours like breast and lung cancer
354. LATANOPROST	To treat increased pressure inside the eye
355. LEFLUNOMIDE	Antirheumatic drug

Table 3 continued...

Table 3 continued...

356. LENALIDOMIDE	Anticancer drug to treat multiple myeloma and myelodysplastic syndromes
357. LENVATINIB MESYLATE	Anticancer drug
358. LERCANIDIPINE HCL	Cardiovascular antihypertensive drug to treat high BP
359. LETROZOLE	Antiestrogen drug to treat postmenopausal women with breast cancer
360. LEUPROLIDE ACETATE	To treat the symptoms of advanced prostate cancer
361. LEVALBUTEROL HCL	Bronchodilator ,sympathomimetic beta-2 adrenergic receptor agonist
362. LEVETIRACETAM	Anticonvulsant to treat epilepsy
363. LEVOCETIRIZINE DIHYDROCHLORIDE	Antihistaminic drug
364. LEVODOPA	To treat Parkinson's disease
365. LEVOFLOXACIN HEMIHYDRATE	Broad-spectrum fluoroquinolone antibiotic
366. LEVOMEPROMAZINE MALEATE	Antipsychotic with strong analgesic, hypnotic and antiemetic properties used to treat refractory nausea unassociated with chemotherapy
367. LEVOMILNACIPRAN	Antidepressant
368. LIDOCAINE	Local anesthetic
369. LINAGLIPTIN	Antidiabetic drug
370. LINEZOLID	Antibiotic
371. LOPERAMIDE HYDROCHLORIDE	Antiperistaltic drug ,used to treat diarrhea
372. LOPINAVIR	Antiretroviral drug to treat HIV
373. LORATIDINE	Antihistamine to treat allergies
374. LORAZEPAM	Anxiolytic and anticonvulsant drug
375. LORMETAZEPAM	Hypnotic and sedative drug
376. LORNOXICAM	Nonsteroidal anti-inflammatory drug
377. LOSARTAN POTASSIUM	ACE-II receptor antagonist used to treat high BP
378. LOTEPREDNOL ETABONATE	To treat certain eye conditions due to inflammation or injury
379. LOVASTATIN	Cardiovascular drug cholesterol lowering
380. LOXAPINE SUCCINATE	Anxiolytic drug
381. LULICONAZOLE	Antifungal drug
382. LURASIDONE HCL	Anti-psychotic drug
383. MARAVIROC	Antiretroviral drug to treat HIV
384. MEBENDAZOLE	Anti-parasitic drug
385. MEBEVERINE HYDROCHLORIDE	Anti-spasmodic drug
386. MECLIZINE HCL	Antihistaminic drug with anti-emetic and sedative properties
387. MECONAZOLE BASE/NITRATE	Antifungal drug

Table 3 continued...

Table 3 continued...

388. MELITRACEN HCL	Antidepressant
389. MELOXICAM	Non-steroidal anti-inflammatory drug
390. MELPHALAN HCL	Chemotherapeutic anti-cancer drug
391. MEMANTINE HYDROCHLORIDE	Alzheimer's disease treatment
392. MEPROBAMATE	Anxiolytic drug to treat anxiety disorders
393. MERCAPTOPURINE	Anticancer drug to treat cancer and autoimmune diseases
394. MESALAMINE/MESALAZINE	To treat mild to moderate ulcerative colitis
395. MESNA	Used in those taking cyclophosphamide or ifosfamide to decrease the risk of bleeding from the bladder
396. METFORMIN HCL	Antidiabetic drug
397. METHOCARBAMOL	To treat muscle spasms/pain
398. METHOHEXITAL	To induce deep sedation or in general anesthesia for surgery
399. METHYLPHENIDATE HCL	Stimulant medication to treat attention deficit hyperactivity disorder and narcolepsy
400. METHYL PREDNISOLONE ACETATE/ HEMISUCCINATE/ SODIUM SUCCINATE	Synthetic glucocorticoid, prescribed for its anti-inflammatory and immunosuppressive effects
401. METHYLSCOPALAMINE BROMIDE [Also known as METHSCOPOLAMINE BROMIDE]	Used as adjunctive therapy for the treatment of peptic ulcer
402. METOCLOPRAMIDE HYDROCHLORIDE	To treat stomach and esophageal problems
403. METOLAZONE	Diuretic, antihypertensive
404. METOPROLOLTARTRATE/ SUCCINATE	Beta blocker treating high BP
405. METRONIDAZOLE	An antibiotic and antiprotozoal medication
406. MEXILETINE HCL	Cardiovascular-to treat abnormal heart rhythms
407. MICAFUNGIN SODIUM	Antifungal drug
408. MICONAZOLE BASE/NITRATE	Antifungal drug
409. MIDAZOLAM MALEATE	Anaesthetic and sedative
410. MIDODRINE HCL	Used as a peripheral vasoconstrictor to treat certain hypotensive states
411. MILBEMYCIN OXIME	Veterinary parasitic drug
412. MILNACIPRAN HCL	Antidepressant ,selective serotonin and norepinephrine reuptake inhibitor
413. MINACIPRAN HCL	Antidepressant
414. MINOXIDIL	Antihypertensive vasodilator, used to treat high BP

Table 3 continued...

Table 3 continued...

415. MIRABEGRON	To treat overactive bladder
416. MISOPROSTOL	Anti-ulcerant drug
417. MITOMYCIN/MITOMYCIN C	Anticancer chemotherapy drug
418. MOMETASONE FUMERATE/ FUMERATE MONOHYDRATE	A steroid drug to treat certain skin conditions
419. MONTELUKAST SODIUM	Anti-asthmatic drug
420. MODAFINIL	To treat sleepiness, reduces extreme sleepiness due to narcolepsy and other sleep disorders
421. MOEXIPRIL HCL	Cardiovascular ACE inhibitor to treat high BP
422. MOMETASONE FUROATE/ FUROATE MONOHYDRATE	Steroid used to treat nasal symptoms such as congestion, sneezing, and runny nose
423. MONOSULFIRAM	Ectoparasiticide, to treat and prevent scabies
424. MONTEKULAST	Anti-asthmatic drug
425. MOXIFLOXACIN HYDROCHLORIDE	Antibacterial drug -fluoroquinolone family
426. MUPIROCIN / CALCIUM	Inhibits bacterial protein synthesis , active against gram-positive staphylococci and streptococci, used in skin disorders, nasal infections, and wound healing
427. MYCOPHENOLATE MOFETIL/ SODIUM	Immunosuppressive drug
428. NABUMETONE	Nonsteroidal anti-inflammatory drug
429. NAPHAZOLINE HYDROCHLORIDE	Decongestant used to relieve symptoms of redness, puffiness and watering of eyes
430. NARATRIPTAN HCL	To treat vascular headaches and migraine
431. NATEGLINIDE	Antidiabetic drug
432. NEBIVOLOL HCL	Beta blocker , used for treating high BP
433. NEVIRAPINE ANHYDROUS/ HEMIHYDRATE	Antiretroviral drug used to treat HIV
434. NEOSTIGMINE METILSULFATE	Used to treat myasthenia gravis, Ogilvie syndrome and urinary retention
435. NICARDIPINE HCL	Cardiovascular drug used to treat BP and to control angina
436. NICOTINE/ POLACRILEX / RESINATE / DITARTRATE DIHYDRATE	Used to help people quit smoking cigarettes
437. NICORANDIL	Vasodilator
438. NIFEDIPINE	Cardiovascular drug used to treat angina, high BP, Raynaud's phenomenon, and premature labor
439. NILOTINIB	Anticancer drug

Table 3 continued...

Table 3 continued...

440. NITAZOXANIDE	To treat diarrhea caused by certain parasite infections
441. NITRAZEPAM	Anticonvulsant and hypnotic
442. NITROFURANTOIN/ MONOHYDRATE	Antibacterial drug, inhibits bacterial DNA, RNA, and cell wall protein synthesis
443. NITROXYNIL	Veterinary anthelmintic drug
444. NIZATIDINE	Histamine H2 receptor antagonist, inhibits stomach acid production. Used to treat peptic ulcer disease and gastroesophageal reflux dise
445. NORTRIPTYLINE HCL	Antidepressant
446. OBETICOLIC ACID	To treat primary biliary cholangitis
447. OCTREOTIDE ACETATE	To control symptoms such as diarrhea or flushing in patients with tumors such as carcinoid, pancreatic islet cell tumors, gastrinoma, or vasoactive intestinal peptide-secreting tumors
448. O-DESMETHYL VENLAFAXINE SUCCINATE MONOHYDRATE	Anti-depressive Agents
449. OFLOXACIN	Quinolone antibacterial drug
450. OLANZAPINE	Antipsychotic drug used to treat schizophrenia and bipolar disorder
451. OMETRAZOLE	A proton-pump inhibitor to treat gastroesophageal reflux disease , peptic ulcers , and Zollinger–Ellison syndrome
452. OLMESARTAN MEDOXOMIL	Cardiovascular drug to treat high BP
453. OLOPATADINE HCL	To decrease the symptoms of allergic conjunctivitis and allergic rhinitis
454. OLSALAZINE SODIUM	Anti-inflammatory drug to treat ulcerative colitis
455. OLANZAPINE	Antipsychotic drug used to treat schizophrenia and bipolar disorder
456. OLMESARTAN MEDOXOMIL	Cardiovascular drug to treat high BP, heart failure and diabetic kidney disease
457. OLOPATADINE HCL	To treat allergic conjunctivitis and allergic rhinitis of eyes
458. OMEORAZOLE//MAGNESIUM/ SODIUM	Proton-pump inhibitor
459. ONDANSETRON HYDROCHLORIDE DIHYDRATE	To prevent nausea and vomiting caused by cancer chemotherapy, radiation therapy, and surgery
460. ORLISTAT	Prevents fat absorption from intestine
461. ORPHENADRINE CITRATE	Anticholinergic drug
462. OSELTAMIVIR PHOSPHATE	Anti-viral drug
463. OXALIPLATIN	Anticancer drug
464. OXAZEPAM	Anxiolytic drug
465. OXCARBAZEPINE	Anticonvulsant

Table 3 continued...

Table 3 continued...

466. OXPENTIFYLLINE / PENTOXYFYLLINE	To treat muscle pain in people with peripheral artery disease
467. OXYBUTYNIN HYDROCHLORIDE	Anticholinergic agent with antispasmodic activity, used to treat overactive bladder
468. OXYCLOZANIDE	Veterinary drug , used to treatment fascioliasis in ruminants
469. OXYMETAZOLINE HYDROCHLORIDE	Nasal decongestant
470. OXYTETRACYCLINE DIHYDRATE/HCL	Antibiotic
471. PACLITAXEL	Anticancer drug to treat multiple types of cancers
472. PALIPERIDONE/PALMITATE	Anti-psychotic , to treat schizophrenia
473. PALONOSETRON HCL	Used for chemotherapy-induced nausea and vomiting control
474. PAMIDRONATE DISODIUM PENTAHYDRATE	Used to prevent osteoporosis
475. PANTOPRAZOLE SODIUM/ SODIUM SESQUIHYDRATE	A proton pump inhibitor
476. PARACETAMOL	Antipyretic drug
477. PAROXETINE HYDROCHLORIDE	Antidepressant drug
478. PAZOPANIB / HCL	Anticancer drug to treat advanced renal cell carcinoma
479. PEMETREXED DISODIUM HEMIPENTAHYDRATE / DIPOTASSIUM NONAHYDRATE	Chemotherapy in multiple types of cancer
480. PERAMPANEL	An antiepileptic drug
481. PERINDOPRIL TERT-BUTYLAMINE/ERBUMINE/ ARGININE	Cardiovascular drug to treat high BP
482. PERPHENAZINE	Antipsychotic drug.
483. PHENAZOPYRIDINE HYDROCHLORIDE	Used to relieve pain , irritation, or urgency caused in urinary tract
484. PHENTERMINE HCL	Used together with diet and exercise to treat obesity, in people with risk factors such as high blood pressure, high cholesterol, or diabetes.
485. PHENYLEPHRINE HYDROCHLORIDE	Used as a decongestant, to increase blood pressure,to relieve hemorrhoids ,and to dilate the pupil
486. PIMAVANSERIN TARTRATE	Antipsychotic to treat Parkinson's disease
487. PIMECROLIMUS	Topical calcineurin inhibitors with immune-modulating and anti-inflammatory properties
488. PINAVERIUM BROMIDE	To treat symptoms of irritable bowel syndrome, stomach pain, irregular bowels and bloating.

Table 3 continued...

Table 3 continued...

489. PINDOLOL	Antihypertensive drug
490. PIOGLITAZONE HYDROCHLORIDE	Antidiabetic drug
491. PIRFENIDONE	To treat mild-to-moderate idiopathic pulmonary fibrosis
492. PIROXICAM	Nonsteroidal anti-inflammatory drug
493. PITAVASTATIN CALCIUM	Blood cholesterol lowering medication
494. PITOFENONE HCL	Anticholinergic drug
495. PLERIXAFOR	An immunostimulant used to mobilize hematopoietic stem cells in cancer patients into the bloodstream
496. POLICRESULEN 50%	Used as a topical hemostatic and antiseptic in lesions of the mucous membranes
497. POMALODOMIDE	To treat certain cancers
498. POSACONAZOLE	Anti-fungal drug
499. PRALATREXATE	Anticancer drug with immunosuppressive properties
500. PRAMIPEXOLE DI-HCL MONOHYDRATE	Parkinson's disease treatment
501. PRAMIRACETAM	Central nervous system stimulant to improve memory and to correct attention deficits in aging people
502. PRASUGREL HYDROCHLORIDE/ BASE	Cardiovascular drug-platelet inhibitor
503. PRAVASTATIN SODIUM	Cardiovascular drug for cholesterol lowering
504. PRAZEPAM	Anxiolytic drug
505. PRAZIQUANTEL	Broad spectrum anthelmintic drug
506. PREDNISOLONE ACETATE/ SODIUM PHOSPHATE/ HEMISUCCINATE	Steroid drug to treat certain types of allergies, inflammatory conditions, autoimmune disorders, and cancers
507. PREGABALIN	To treat pain caused by nerve damage , pain caused by spinal cord injury, pain with fibromyalgia and to treat certain types of seizures
508. PRIDINOL MESYLATE	Muscle relaxant
509. PRIMIDONE	Barbiturate, anti-epileptic drug to treat partial and generalized seizures, also essential tremors
510. PROCHLORPERAZINE EDISYLATE /MALEATE	Antipsychotic drug used to treat severe nausea and vomiting
511. PROGUANILHCL	Antimalarialdrug
512. PROMETHAZINE HYDROCHLORIDE	To treat allergies, trouble sleeping, and nausea
513. PROPAFENONE HCL	Cardiovascular drug for anti-arrhythmic medication
514. PROPIOMAZINE MALEATE	Sedative and hypnotic drug

Table 3 continued...

Table 3 continued...

515. PROPRANOLOL HYDROCHLORIDE	Cardiovascular drug, a beta blocker used to treat high BP
516. PROPOFOL	Used in general anesthesia, sedation for mechanically ventilated adults and procedural sedation
517. PYRANTEL PAMOATE	Anthelmintic medication.
518. PYRAZINAMIDE	Anti TB drug
519. QUETIAPINE FUMERATE	Antipsychotic medication to treat schizophrenia and acute episodes of bipolar disorder
520. QUINAPYRAMINE CHLORIDE/ SULFATE	Veterinary ,trypanocidal agent
521. QUINAPRIL HCL	Cardiovascular drug to treat high BP
522. QUININE DIHYDROCHLORIDE / SULPHATE	Antimalarial drug
523. RABEPRAZOLE SODIUM	A proton pump inhibitor
524. RAFOXANIDE	To treat flukes and roundworms in cattle
525. RALOXIFENE HCL	Anti-osteoporosis drug
526. RALTEGRAVIR POTASSIUM	Anti-retroviral drug to treat HIV
527. RAMIPRIL	Cardiovascular drug to treat high BP
528. RANITIDINE BASE / HCL	Decreases stomach acid production. Used in treatment of peptic ulcer disease, gastroesophageal reflux disease etc.
529. RANOLAZINE	Cardiovascular drug to treat heart related chest pain
530. RASAGILINE MESYLATE/ TARTRATE	To treat Parkinson's disease
531. REBAMIPIDE	Anti-ulcerant drug used for healing gastroduodenal ulcers, and treatment of gastritis.
532. REGORAFENIB	Anticancer drug to treat multiple tumour types
533. REPAGLINIDE	Antidiabetic drug
534. RESERPINE	To treat high BP
535. RICOBENDAZOLE	Anthelmintic for veterinary use
536. RIFABUTIN	Anti-TB drug
537. RIFAMPICIN	Anti-TB drug
538. RIFAPENTINE	Anti-TB drug
539. RIFAXIMIN	To treat travelers' diarrhea, irritable bowel syndrome, and hepatic encephalopathy
540. RILUZOLE	To treat amyotrophic lateral sclerosis
541. RISEDRONATE SODIUM	To treat Paget's disease that weakens bones
542. RISPERIDONE	Treatment of mania and schizophrenia
543. RITONAVIR	Antiretroviral drug to treat HIV

Table 3 continued...

Table 3 continued...

544. RIVASTIGMINE BASE / TARTRATE	Alzheimer's disease and Parkinson's disease
545. RIVAROXABAN	Anticoagulant medication
546. RIZATRIPTAN BEZOATE	Treatment of migraine headaches
547. ROPIVACAINE HCL	Local anesthetic drug
548. ROMIDESPIN	Anticancer drug
549. ROPINIROLE HCL	Parkinson's disease
550. ROSIGLITAZONE MALEATE	Antidiabetic drug (raises risks of heart disease)
551. ROSUVASTATIN / CALCIUM	Cardiovascular antihyperlipidimic drug
552. ROXITHROMYCIN	Antibiotic-semi-synthetic macrolide
553. RUFINAMIDE	Anticonvulsant
554. RUPATADINE FUMERATE	Antihistaminic drug
555. SALBUTAMOL SULFATE	Causes relaxation of airway smooth muscle,used to treat asthma and chronic obstructive pulmonary disease
556. SAQUINAVIR MESYLATE	Antiretroviral drug to treat HIV
557. S-METHOPRENE	Optically active insect juvenile hormone analog , used as an insecticide
558. SALMETEROL XINAFOATE	Anti asthmatic drug
559. SAXAGLIPTIN HCL	Antidiabetic drug
560. SCOPOLAMINE HBR	Used in premedication in anesthesia and for the prevention of nausea and vomiting
561. SERTACONAZOLE NITRATE	Anti-fungal drug
562. SERTRALINE HYDROCHLORIDE	Antidepressant
563. SEVEAMER CARBONATE/HCL	Antinephrotic drug for treating chronic kidney disease
564. SEVELAMER HCL / CARBONATE	Used to lower high blood phosphorus (phosphate) levels in patients who are on dialysis due to severe kidney disease
565. SILDENAFIL CITRATE	To treat erectile dysfunction
566. SILODOSIN	To treat benign prostatic hyperplasia
567. SILVER SULFADIAZINE	Used as a topical antibacterial agent on wounds, burns etc
568. SIMETHICONE	Anti-flatulence medication
569. SIMVASTATIN	Cardiovascular hypolipidimic drug
570. SIROLIMUS	Immunosuppressant macrolide
571. SITAGLIPTIN PHOSPHATE/ PHOSPHATE ANHYDRIDE/ PHOSPHATE MONOHYDRATE/ MONOHYDRATE	Antidiabetic drug

Table 3 continued...

Table 3 continued...

572. SODIUM OXYBATE	CNS depressant
573. SODIUM POLYSTYRENE SULPHONATE	To treat hyperkalemia in kidney disease
574. SODIUM VALPROATE	To treat epilepsy and bipolar disorder
575. SOLIFENACIN SUCCINATE	Anticholinergic and antispasmodic agent to treat urinary incontinence
576. SORAFENIB TOSYLATE	Anticancer drug
577. SPIRONOLACTONE	Diuretic drug
578. STAVUDINE	Antiretroviral drug to treat HIV
579. STRONTIUM RANELATE	Antiosteoporotic agent
580. SUCCINYL CHOLINE CHLORIDE	Muscle relaxant
581. SUGAMMADEX SODIUM	For reversal of neuromuscular blockade induced by rocuronium and vecuronium in adults undergoing surgery
582. SULFAMETHOXAZOLE	To treat bacterial infection
583. SUMATRIPTAN SUCCINATE	To treat migraine and cluster headaches
584. SUNITINIB MALATE	Anticancer drug
585. TACROLIMUS/ MONOHYDRATE	Immunosupressive drug
586. TADALAFIL	To treat erectile dysfunction , benign prostatic hyperplasia and pulmonary arterial hypertension
587. TAMOXIFEN CITRATE	To treat breast cancer
588. TAMSULOSIN HYDROCHLORIDE	To treat benign prostatic hyperplasia and chronic prostatitis
589. TAPENTADOL HYDROCHLORIDE	A novel analgesic
590. TAZAROTENE	To reduce fine wrinkles and dark and light spots on face
591. TEICOPLANIN	Antibiotic , to treat serious infections caused by Gram-positive bacteria
592. TEMAZEPAM	Sedative, and hypnotic
593. TELMISARTAN	Cardiovascular drug to treat high BP
594. TEMOZOLOMIDE	Anticancer drug for first-line treatment for glioblastoma
595. TEMSIROLIMUS	Treatment of renal cell carcinoma
596. TENELIGLIPTIN	Anti-diabetic drug
597. TENOFOVIR DISOPROXIL FUMARATE/DIISOPROPYL PHOSPHATE/ALAFAMIDE FUMERATE	Anti-retroviral drug always used in combination with other drugs for treating HIV
598. TERAZOSIN HCL DIHYDRATE	Cardiovascular drug, vesodilator , decreases low-density lipoproteins and triglycerides while increasing high-density lipoproteins

Table 3 continued...

Table 3 continued...

599. TERBINAFINE HYDROCHLORIDE	Antifungal drug
600. TERBUTALINE SULPHATE	Terbutaline, a beta agonist , used to treat wheezing, shortness of breath, and chest tightness caused by asthma and chronic bronchitis
601. TERIFLUNOMIDE	Immunomodulator drug
602. TERIPARATIDE	Used to treat some forms of osteoporosis
603. TERLIPRESSIN ACETTE	Vasopressin analogue used to treat low blood pressure
604. TETRACYCLINE HCL	Antibiotic
605. TETRABENAZINE	To decrease the uncontrollable movements (chorea) caused by Huntington's disease
606. THALIDOMIDE	Sedative drug
607. THIABENDAZOLE	Anthelmintic agent
608. THIOCOLCHICOSIDE	Muscle relaxant
609. THIOTEPA	Anticancer drug
610. TICAGRELOR	Cardiovascular antiplatelet medicine
611. TIEMONIUM METHYL SULFATE	Antispasmodic drug
612. TIMOLOL MALEATE	To treat glaucoma
613. TIOCONAZOLE	Antifungal drug
614. TIPIRACIL HCL	Anti-cancer drug
615. TIZANIDINE HCL	To treat muscle spasticity due to spinal cord injury or multiple sclerosis
616. TOFACITINIB CITRATE	To treat Rhematoid Arthritis
617. TOLDIMPHOS SODIUM	To treat reproduction diseases and developmental and nutritional disorders of young animals
618. TOLFENAMIC ACID	To treat migraines and severe headaches
619. TOLPERISONE HYDROCHLORIDE	Muscle relaxant drug
620. TOLTERODINE TARTRATE	To treat frequent urination, urinary incontinence or urinary urgency
621. TOPIRAMATE	To treat epilepsy and prevent migraine
622. TOPOTECAN HCL	Chemotherapeutic drug against cancers
623. TORASEMIDE ANHYDROUS(Also known as TORSEMIDE	Diuretic drug used to treat fluid overload due to heart failure, kidney disease, and liver disease and high blood pressure
624. TRAMADOL HCL	An opioid pain medication used to treat moderate to moderately severe pain
625. TRANDOLAPRIL	Cardiovascular drug ACE –inhibitor to treat high BP
626. TRANEXAMIC ACID	To treat or prevent excessive blood loss for various reasons

Table 3 continued...

Table 3 continued...

627. TRANYLCYPROMINE SULFATE	Antidepressant drug
628. TRAZODONE HCL	Antidepressant drug
629. TREOSULFAN	Belongs to alkylating agents, used in conditioning treatment prior to allogeneic haematopoietic stem cell transplantation
630. TRIAMCINOLONE ACETONIDE	Synthetic corticosteroid used to treat various skin conditions, to relieve the discomfort of mouth sores, various joint conditions ,allergic rhinitis etc
631. TRIAZOLAM	Sedative and hypnotic drug
632. TRICLABENDAZOLE	To treat fascioliasis and paragonimiasis
633. TRIENTINE HCL	A metal chelating agent with potential anti-angiogenic activity used to treat Wilson's disease
634. TRIFLURIDINE	An anti-herpesvirus antiviral drug, used primarily on the eye
635. TRIMETHOBENZAMIDE HCL	Antiemetic drug
636. TRIPROLIDINE HCL MONOHYDRATE	Antihistamine , used for to treat uticaria, rhinitis, and pruritic skin disorders
637. TROPICAMIDE	Anti-cholinergic drug
638. TROSPIUM CHLORIDE	Antidepressant to treat certain mental/mood disorders
639. VALACYCLOVIR HCL	Antiviral drug to treat herpes, herpes zoster (shingles) and varicella zoster
640. VALPROIC ACID/SODIUM VELPROATE	To treat epilepsy and bipolar disorder and to prevent migraine headaches
641. VALSARTAVANCOMYCIN HCLN	Cardiovascular drug to treat high BP
642. VANCOMYCIN HCL	Antibiotic to treat multiple bacterial infection+
643. VARDENAFIL HYDROCHLORIDE	To treat ejectile disfunction
644. VARENICLINE TARTRATE	Used for cessation of Smoking
645. VELPATASVIR	Antiviral drug to treat hepatitis –C infection
646. VENLAFAXINE HCL	Antidepressant
647. VERAPAMIL HCL	Anti-hypertensive drug
648. VIGABARTIN	Anticonvulsant
649. VILAZODONE HCL	Antidepressant
650. VILDAGLIPTIN	Antidiabetic drug
651. VINBLASTIN SULPHATE	Chemotherapy medication against cancer
652. VINCAMINE	Used to treat primary degenerative and vascular dementia
653. VINCRISTINE SULPHATE	Chemotherapy medication against cancer
654. VINPOCETINE	To treat cerebrovascular disorders such as stroke and dementia
655. VORICONAZOLE	Anti-fungal drug
656. VORTIOXETINE HBR	Anti-depressant drug

Table 3 continued...

Table 3 continued...

657. XYLOMETAZOLINE HYDROCHLORIDE	To reduce symptoms of nasal congestion, allergic rhinitis, and sinusitis
658. YOHIMBINE HCL[Also known as QUEBRACHINE]	To treat peptic ulcers
659. ZALEPLON	Sedative-hypnotic to treat insomnia
660. ZALTOPROFEN	A non-steroidal anti-inflammatory drug
661. ZIDOVUDINE	Antiretroviral drug to treat HIV
662. ZOLEDRONIC ACID/ ZOLEDRONATE	To treat a number of bone diseases
663. ZILEUTION	To treat asthma
664. ZIPRASIDONE HCL	Antipsychotic drug
665. ZOLMITRIPTAN	Treatment of migraine attacks
666. ZOLPIDEM TARTRATE	To treat sleeping disorder/ insomnia
667. ZOLMITRIPTAN	Anti-migraine drug
668. ZONISAMIDE	Anticonvulsant drug
669. ZOPICLONE	A non-benzodiazepine used to treat difficulty in sleeping

Source: Author's compilation

As many as 669 generic APIs have been identified and placed in the Table-3.
These 669 generic APIs of Table-3 have been classified, based on the identification of the curative and remedial applications of these drugs, into the following twenty therapeutic categories:

1. **Antiviral drugs, including anti-HIV drugs; anti-HBV drugs; and anti-HCV drugs**
2. **Anticancer drugs**
3. **Drugs for treating cardiovascular diseases including anti-thrombolytic drugs; anti-coagulants; anti-lipidimic drugs; anti-platelet drugs; drugs for treating high blood pressure; COPD drugs etc.**
4. **Anti-gout drugs**
5. **Antihistamines**
6. **Proton pump inhibitors/anti-ulcerants/ anti-emetics/ prokinetic agents**
7. **Anti-diabetic drugs**
8. **Anti-depressants/benzodiazepines/psychosomatics and attention deficit hyperactivity disorder drugs**
9. **Analgesics, Non-steroidal anti-inflammatory drugs**
10. **Analgesics, Non-steroidal anti-inflammatory drugs**
11. **Anti-spasmodic drugs and muscle relaxants**

12. **Anti-vomit inducers**
13. **Anti-psoriasis drugs**
14. **Anti-bacterial drugs**
15. **Anthelmintic Drugs**
16. **Anti-fungal drugs**
17. **Anti-malarial drugs**
18. **Multiple veterinary drugs**
19. **Drugs for the treatment of Parkinson's disease and Alzheimer's disease**
20. **Corticosteroids and all other steroids**

The exports data of the major number of these generic APIs were collected with assistance from the officers of Research and Information System for Developing Countries (RIS),New Delhi ; the data were obtained from the information published by the Indian Ministry of Commerce, which uses the Harmonized System (HS) Codes [a standardized numerical method of classifying traded products, and are administrated by the World Customs Organization (WCO)]. The HS Code provides information on certain selected bulk drugs by individual mane while most others are clubbed together by the WCO on some basis, not know to the author. Such clubbing prevents access to the exports data of each individual export of generic API. Nevertheless, the data collected and compiled from the published information by the Indian Government under the HS CODE, and rearranged under the above twenty therapeutic categories, as are placed below in Table-4.

Table 4: Exports of generic APIs from India during 2019 and 2020: (US $ million)

1. Antiviral drugs, including anti-HIV drugs; anti-HBV drugs; and anti-HCV drugs

HS CODE	DESCRIPTION	2019	2020

2. Anticancer drugs

HS CODE	DESCRIPTION	2019	2020
30049041	Cyclophosphamide	2.33	3.69
30049043	Bincristine and vinblastine	0.66	0.75
30049044	Paclitaxel and docetaxel	55.29	62.36
30049045	Etoposide	4.01	4.04
30049046	Actinomycin dactinomycin and doxorubicin	72.28	97.51
30049047	L-asparaginase, cisplatin and carboplatin	35.65	40.59
30049048	Tamoxifen	4.60	4.29
SUB-TOTAL		**174.82**	**213.23**

3. Drugs for treating cardiovascular diseases including anti-thrombolytic drugs; anti-coagulants; anti-lipidimic drugs; anti-platelet drugs; drugs for treating high blood pressure; COPD drugs etc.

HS CODE	DESCRIPTION	2019	2020
29051420	Salbutamol sulphate	6.52	5.65
29420013	Nifedipine	3.57	4.11
30049072	Verapamil, nifedipine, amlodipine and lacidipine	92.19	108.66
30049073	Losartan	86.96	147.24
30049074	Propranolol, metoprolol, atenolol and labetalol	121.85	125.24
30049075	Prazosin, terazosin, phentolamine and phenoxybenzamine	0.42	0.97
30049076	Clonidine, methyldopa	7.73	9.49
30049077	Hydralazine, minoxidil and diazoxide	6.04	10.34
30049091	Salbutamol, terbutaline, ephedrine, salmeterol and methyl xanthimes	57.76	49.54
29420027	Atenolol, propronalol	10.45	11.42
30049071	Captopril, enalapril, lisinopril, perindopril and ramipril	119.04	147.70
SUB-TOTAL		**512.53**	**620.36**

4. Anti-gout drugs

HS CODE	DESCRIPTION	2019	2020

5. Antihistamines

HS CODE	DESCRIPTION	2019	2020

6. Proton pump inhibitors/anti-ulcerants/ anti-emetics/ prokinetic agents

HS CODE	DESCRIPTION	2019	2020
29225090	Other frusemide aminodial domperidone	110.68	109.48
29420014	Ranitidine	51.10	27.06
30049033	Cimetidine, rantidine, nizatidine and roxatidine	77.37	40.05
30049034	Omeprazole and lansoprazole	246.52	247.43
30049035	Dicyclomine, metoclopramide and dexamethasone and ondansetron	55.66	54.43
SUB-TOTAL		**541.33**	**478.45**

7. Anti-diabetic drugs

HS CODE	DESCRIPTION	2019	2020

8. Anti-depressants/benzodiazepines/psychosomatics and attention deficit hyperactivity disorder drugs

HS CODE	DESCRIPTION	2019	2020
29420024	Imipramine hcl	0.60	1.17
29337200	Clobazam (inn) and methypryldn (inn)	2.00	1.64
29241100	Meprobamate (inn)	0.06	0.22
SUB-TOTAL		**2.66**	**3.03**

9. Analgesics, Non-steroidal anti-inflammatory drugs

HS CODE	DESCRIPTION	2019	2020
29222933	Para acetyl aminophenol(paracetamol)	98.51	79.34
30049063	Ibuprofen with or without paracetamol or other compounds	167.83	218.86
30049066	Mephenamic acid, dactofenac sodium, piroxicam, tenoxicam and meloxicam	64.81	79.19
30049067	Ketorolac, nimesulide, nabumetone and nefopam	91.38	95.95
30049081	Phenobarbitone,mephobarbitone,primidone, phenyt oin,carbamazpin,ethosucimid, valporicacid, diazepa, lamotrigin, gabapentin	336.86	303.26
SUB-TOTAL		**759.39**	**776.60**

10. Anti-spasmodic drugs and muscle relaxants

HS CODE	DESCRIPTION	2019	2020

11. Anti-vomit inducers

HS CODE	DESCRIPTION	2019	2020

12. Anti-psoriasis drugs

HS CODE	DESCRIPTION	2019	2020

13. Anti-bacterial drugs

HS CODE	DESCRIPTION	2019	2020
	ANTIBIOTICS **(Tertacyclines / Macrolides/ Glycopeptides/Quinolones/betalactams/others)**		
294130	Tetracyclines and their derivatives, salts thereof:	2.40	2.19
30042042	Oxytetracycline	1.81	0.83
30042061	Erythromycin in capsules, injections, ointments etc.	14.51	15.87
30042062	Roxithromycin	1.04	1.89
30042063	Clarithromycin	27.03	24.9
30042064	Azithromycin	55.1	65.05
30042096	Vancomycin	65.31	49.97
30042034	Ofloxacin	7.25	7.19
29414000	Chloramphenicol & its drvtvs ,salts thereof	3.24	1.97
SUB-TOTAL		**177.69**	**169.86**
	ANTI-TUBERCULAR DRUGS		
29419011	Rifampicin	3.16	9.35
29419019	Other rifampicin and its salts	2.06	2.4
30042092	Rifampicin	1.09	0.57
30049052	Rifampicin	2.79	6.02
29051410	Ethambutol, ethambutol hcl	10.86	10.08
30042094	Ethambutol	0.72	0.85
30049053	Pyrazinamide and ethambutol	5.58	5.66
29242960	Pyrazinamide(pyrazine carboxamide)	4.38	3.14
SUB-TOTAL		**30.64**	**38.07**
	ANTI-LEPROCY DRUGS		
30049055	Dapsone (dds), acedapsone (dadds), solopsone and clofazimine	1.18	0.81
SUB-TOTAL		**1.18**	**0.81**
	ANTI-DIARRIAL / ANTI-PROTOZOAL/ANTI-DYSENTRY DRUGS		
29420031	Diloxanide furoate anti-protozoal drug	3.60	3.23
29420033	Oxyclozanide	7.74	6.92
29420034	Famotidine	10.79	10.11
29420090	Other diloxanide furoate, famotidine nes	946.82	962.22
30049022	Metronidazole-formulations single and in combination with furazolidone & diloxanide furoate.	42.08	42.28
SUB-TOTAL		**1011.03**	**1024.76**

14. Anthelmintic Drugs

HS CODE	DESCRIPTION	2019	2020
29332930	Mebendazole	5.21	5.45
SUB-TOTAL		**5.21**	**5.45**

15. Anti-fungal drugs

HS CODE	DESCRIPTION	2019	2020

16. Anti-malarial drugs

HS CODE	DESCRIPTION	2019	2020
30049056	Chloroquine, amodiaquine, mefloquine, quinine, chloroguamide, pyrimethamine	9.71	10.41
29392020	Quinine hydrochloride	3.33	2.25
SUB-TOTAL		**13.04**	**12.66**

17. Multiple veterinary drugs

HS CODE	DESCRIPTION	2019	2020
30039034	Anaesthetic agents used in human or veterinary medicine or surgery	33.14	40.15
30049029	Other anthelmintics drugs; antiamoebic and other antiprotozoal/antifungal drugs	190.14	215.12
30049075	Prazosin, terazosin, phentolamine and phenoxybenzamine	0.42	0.99
30049085	Veterinary medicinal preparations n.e.s.	27.07	30.38
SUB-TOTAL		**250.77**	**286.64**

18. Drugs for the treatment of Parkinson's disease and Alzheimer's disease

HS CODE	DESCRIPTION	2019	2020

19. Drugs for the treatment of benign prostatic hyperplasia

HS CODE	DESCRIPTION	2019	2020

20. Corticosteroids and all other steroids

HS CODE	DESCRIPTION	2019	2020
30043912	Prednisolone	15.73	17.32
SUB-TOTAL		**15.73**	**17.32**
GRAND TOTAL (US$ million):		**3490.81**	**3641.79**

It can be seen from the information furnished in Table 4 that the export data of each individual generic API is not reported, the information is too often clubbed together for a group of generic APIs; this is probably done because the individual exports may have been low. It can also be seen that for a number of drugs belonging to the therapeutic categories (a) Antiviral drugs, including anti-HIV drugs; anti-HBV drugs; and anti-HCV drugs ; (b) Antihistamines; (c) Anti-diabetic drugs; (d) Anti-spasmodic drugs and muscle relaxants; (e) Anti-vomit inducers (having antihistaminic and weak anticholinergic action); (f) Anti-psoriasis drugs; (g) Anti-fungal drugs; (h) Drugs for the treatment of Parkinson's disease and Alzheimer's disease; and (i) Drugs for the treatment of benign prostatic hyperplasia, no information was available. Further, certain bulk API such as dexamethasone [a steroid] , ondansetron [a serotonin 5-HT3 receptor antagonist] were clubbed together with "Proton pump inhibitors/anti-ulcerants/ anti-emetics/ prokinetic agents ". This data was the only source for the export of generic APIs, and were used, taking into considerations the above limitations.

The total exports of these generic APIs during the period 2019 and 2020 were available in INR. The INR values have been converted into US$, taking one US$ as equivalent to INR 70. The calculated values of exports of generic APIs worked out to US$ 3490.81 million and US$ 3641.79 million respectively. The total exports of generic APIs during 2018-19 was US$ 3.84 billion, and may have risen to US$ 4.15 billion and US$ 4.48 billion respectively during 2019-20 and 2020-21 , taking into consideration the average annual rise in exports of about 8 per cent . The data presented for the exports of generic APIs for the year 2019 [Table 3], which was US$ 3.49 billion, was about 90.9 per cent of the total exports of APIs during the year. This provides some respite that most of the major exports of generic APIs as captured in Table 4 are exhaustive.

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