Indian Chemical Industry

By A V Rama Rao
Former Director, Indian Institute of Chemical Technology, Hyderabad

https://doi.org/10.51167/acm00035

In early 1940s, I was a young child who suffered several bouts of malaria. The only drug available at the time was quinine which was sold in the local post office. No doubt it helped as a cure, but many also died of malaria. I also realized if anybody contacted TB, they would die in a short time. The other prominent disease was smallpox. If a patient contacts smallpox their survival rate was very slim. People believed that it was due to the curse of the local Goddess, and they would perform rituals, poojas and prayers for eradicating the disease. I can go on mentioning the gamut of the health problems that people were facing during those times. The life expectancy during those years was less than 40 years. Today the situation is totally different. Malaria as well as TB are no more dreadful diseases. They can be cured with proper medication. Smallpox has been almost totally eradicated from the world due to vaccination programs. Thus, the health of humanity has improved, and the life expectancy has gone up well beyond 70 years. How has this happened? This is due to the relentless efforts of chemical and pharmaceutical industries. We now live in a world with lifesaving drugs, where many are available as generics - off patent drugs available at a much affordable price.

Even in India, domestic chemical manufacturers provide various fertilizers, agrochemicals for our food. We use colouring material such as dyes and pigments to colour fabrics and for a variety of other uses. The polymer industry has grown and entered every aspect of our lives, from packing water, milk, and food, for the clothes we wear, furniture, automobiles, machines and electronics we use are made from plastics. The list is long.

*Current Address: 7-102/54, Sai Enclave, Habsiguda, Hyderabad – 500007.

Chemical Industry:

Chemistry is at the center of all the action; atoms form molecules which further aggregate to everything in life. The subject has grown, and its allied industries have evolved to deliver everything that supports our lives.

The global chemical market is worth USD 4.73 trillion, and Europe was the largest producer till recent years with China taking over most of the global chemical production. The German company BASF is the world's largest chemical company. The fast-growing Chinese chemical industry is now valued at over 1.5 trillion US dollars and representing 40% of the global chemical industry revenue.

Chemicals can be broadly divided as large volume or bulk chemicals which include petrochemicals, fertilizers, polymers, etc. and specialty chemicals which are also referred to as fine chemicals which have a relatively higher value and used in making pharmaceutical drugs, dyes, agrochemicals, fragrances, and materials

The Indian chemical industry is valued at over USD 200 billion (3% of the world sales) and likely to reach USD 300 billion by 2025. Drugs and Pharmaceuticals normally form a separate class and generally are not included in the chemical sector. India has played a major role in the production of generic drugs (copies of off-patent branded drugs that have the same chemical composition and intended for the same use as the branded drug).

Before any pharmaceutical company introduces a new drug in the market they patent and protect their product to become the sole manufacturer of the drug for the patent duration (life of a patent is normally 20 years). Once the patent expires, other companies can manufacture the same drug with the same chemical composition and purity, these are referred as generic drugs. Today, India had the distinction of being

Dr. A V Rama Rao

Dr. A.V. Rama Rao was born in 1935 in Guntur, Andhra Pradesh, and received his B.Sc. in 1960 from Bombay University and Ph.D. in 1964 from NCL Pune with Dr. K. Venkataraman. While at NCL, he took a sabbatical leave with Prof E.J. Corey at Harvard University (1975-1977). In 1965 he became a Scientist B at NCL Pune and later was Head of the Organic Chemistry Division there. In 1985, He moved to the CSIR in Hyderabad as a Director and transformed the Regional Research Laboratory (RRL) into the Indian Institute of Chemical Technology (IICT). After retirement in 1995, he founded the A. V. Rama Rao Research Foundation, a non-governmental promoting research and doctoral studies in chemistry, and the Avra Laboratories. This multi-million-dollar pharmaceutical company currently has over 600 employees. Dr. Rama Rao has trained 112 Ph.D. students and published more than 260 papers on the isolation and structural elucidation of plant and insect pigments and synthetic dyes, biologically active natural products such as antitumor antibiotics, macrolides, immunosuppressants, and cyclic peptides. He received the Padma Shri (1991), Padma Bhushan (2016), and the technology award from the World Academy of Sciences (TWAS). He is a fellow of all science academies in India and a fellow of the TWAS.

the second largest producer with USFDA approved drug manufacturing units outside the US. The Indian pharmaceutical companies have filed so far more than 1218 ANDAs (abbreviated new drug application) with the USFDA which amounts 45.5% of all applications. The top 20 Indian pharmaceutical companies constitute 80.5% of these applications and 40% of generic drugs used in USA come from Indian manufacturers. The country also has a well-evolved ecosystem of highly skilled professionals to undertake these tasks required for highly regulated manufacturing. Further, 95% of its domestic bulk drug requirements are met by the local industries ensuring drug prices in India are one of the lowest in the world.

Over the last 5 decades, I dealt extensively with the Indian pharma industry and watched it grow from its infancy to its current leadership position.

Earlier History of the Indian drugs and pharmaceutical industry:

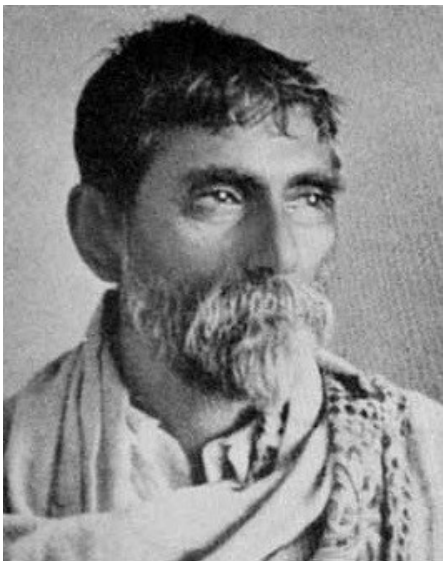
Before the British invaded and took over the country, the Indian medical system relied on traditional Ayurveda and Unani, which were the only indigenous forms that were practiced for the health care and available. The development of the drug industry in India started around a century ago. In 1892, Acharya Prafulla Chandra Ray (P C Ray), started a small manufacturing factory for chemicals and pharmaceuticals named as Bengal Chemicals and Pharmaceuticals in a rented house at "91, Upper Circular Road, Calcutta" with a minimum capital of Indian rupees 700. Ray was keen to exploit the knowledge of ancient Indian medicine by adopting modern methods for manufacturing. The company was converted as a limited company in the name of Bengal Chemicals and Pharmaceutical Works Limited in 1901. It gradually expanded and had undertaken bulk drug production and formulations. In addition, the company was making some perfumes, cosmetics, surgical equipment. Till 1960 the company-maintained leadership in technology after which its sales slowly went down and became sick in 1970. The Government of India nationalized it in December 1980, but it did not recover and once again was declared sick on 14 Jan 1993. Further attempts to revive the company by infusing more money during the Government's 11th five-year plan did not help. Ray also established in 1919 Bengal Immunity Company Limited to produce Sera, vaccines and toxoids, based on their know-how using indigenous raw materials. An important life-saving contribution the company made was the development of an anti-snake venom serum which was effective against the commonly encountered Indian Cobra. The serum was prepared from concentrated and purified plasma obtained from hyper-immunizing horses.

The second major chemical and pharmaceutical company in India was Alembic Chemical Works Company Limited started by B D Amin in 1907 in Baroda with the support of the Maharaja of Baroda. It has grown into a multinational organization and is involved in the manufacture of drugs and intermediates. The company is a leader in macrolide segments of anti-infective drugs and also has expertise in peptide manufacture.

In the US and Europe, modern drug development witnessed a revolution and rapid growth between 1930 to 1960, wherein several breakthroughs were made with the discovery of penicillin and other antibiotics along with the development of synthetic drugs that could treat a gamut of diseases. For example, in early 1930s, Gerhard Domagk of Bayer in Germany tested various azo-dyes against Streptococcal bacteria and discovered Prontosil as an antibacterial agent. In late 1935, he gave it to his dying daughter suffering from a streptococcal infection. She recovered although with a side effect that turned her bright red. Prontosil was not active in Vitro but in Vivo it was converted to Sulphanilamide the main active compound and this discovery gave birth to various sulpha-drugs. He was awarded the the Nobel Prize in 1939.

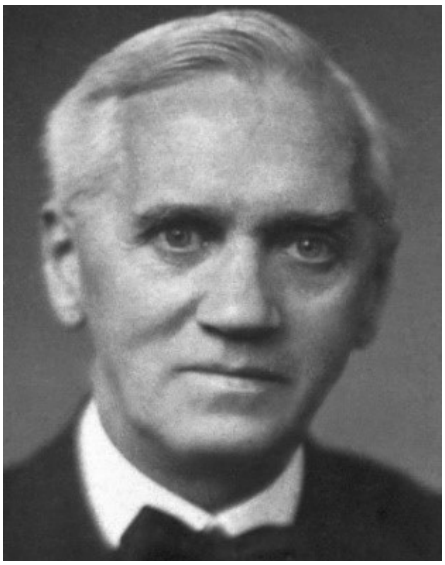
Another major and accidental discovery was Penicillin. Alexander Fleming working at St. Mary's hospital, London in 1928 discovered Penicillin a life-saving antibiotic drug. Penicillin's curative power and therapeutic action was fully identified by Howard Florey and Ernest Boris Chain and finally the drug was mass produced and commercialized in 1941. During the second world war Penicillin was extensively used to treat the wounded soldiers. Currently, Penicillin is more a starting material for the manufacture of several semi-synthetic antibiotics such as Ampicillin and Amoxicillin. During that period several synthetic drugs also entered the market, which include vitamins, hormones, psychotropic drugs, antihistamines, and anesthetics. However, in India before independence most of these drugs were not made and not easily accessible at affordable prices.

Several multinational companies had formulation facilities in India and were using imported active drug substances, these included- Glaxo, Burrows Welcome, Ciba, Roche, Parke-Davis, Merck, Hoechst, and Wyeth.



Acharya Prafulla Chandra Ray (1861 – 1944)

(Gerhard Domagk) Discoverer of sulfa drug



(Alexander Fleming)

These multinational companies operating in India took advantage of the prevailing Indian Patent Act of 1911 and almost all the new drugs introduced in India were priced higher compared to New York or London prices. Realizing the need for affordable health care, the Indian Government encouraged the production of drugs by starting state-owned public-sector units. Thus, Hindustan Antibiotics was started in Pune in 1955 to produce penicillin and streptomycin and their formulations with aid from WHO and UNICEF. Similarly, Indian Drugs and Pharmaceuticals Limited (IDPL) was incorporated in 1961, with the sole objective of creating self-sufficiency through the domestic manufacturing of essential life-saving drugs. IDPL's facility in Hyderabad started manufacturing several synthetic drugs including sulfa drugs and vitamins initially with assistance from the former Soviet Union (USSR) government.

IDPL - Hyderabad played a major role in developing infrastructure for the growth of the Indian drug industry especially the bulk drug industry which involved the mass production of active ingredients. Later some the technical staff left IDPL and started their own companies based on the knowledge that they acquired from IDPL. Several of these former employees went on to become successful entrepreneurs while laying the foundation for the private pharmaceutical industry. Unfortunately, the growth of the private sector led to downfall of the state owned IDPL which was finally liquidated on 9th February 2021 by the Government of India. The city of Hyderabad owes its success and reputation as the pharma capital of India to IDPL. The two states of Andhra Pradesh and Telangana together have 2500 pharma companies with most of them having their headquarters in Hyderabad.

Several Indian companies came together and formed the Indian Drug Manufacturing Association (IDMA) in 1961, with the sole aim of boosting domestic manufacturing. They fought to amend the 1911 Patent Act, a struggle which was culminated in the enactment of the Indian Patent Act of 1970 which was passed by the Indian parliament in September 1972. As a result, "all product patents for drugs and agrochemicals were abolished and only process patents were allowed for a period of 7 years from the date of filing the patent or 5 years from the date of acceptance whichever is earlier". This allowed the Indian pharma industry to begin its journey of drug development and manufacturing. In 1947, the Indian pharma industry had a turnover of Rs.10 crores which had gone up to Rs.360 crores by 1972 but this was just over 1% of the world pharma market value. By 1980's there was phenomenal growth; imports of pharmaceuticals was marginal while India started exporting API's (Generic drugs) and their formulations to various countries.

Indian Institutions and Industry collaboration for developing technologies for lifesaving drugs:

After enacting the new patent law, the then Prime Minister, Mrs. Indira Gandhi who was also the President of the Council for Scientific and Industrial Research (CSIR) instructed all the CSIR Directors, to initiate the development for drugs and agrochemicals and help the Indian chemical industry in technology transfer and commercialization. Dr. B D Tilak, the then Director of National Chemical Laboratory (NCL), Pune, called a meeting of various divisional heads including myself; I happened to be a young project leader in NCL. Dr Tilak stated the Government's intent to initiate work towards the process development for some of the essential drugs. Most of the senior scientists did not take his message seriously and some even refused expressing that they were working in the NCL with a meager salary only for the academic pursuit of fundamental research and if they had to do industrial research, they could as well go to industry and earn a salary at least 10 times higher than what they were being offered in NCL. I was a graduate of Chemical Technology from Bombay University; I realized that the search for innovative solutions to industry related problems could also be done along with basic academic research. I felt finding a new process to produce a drug could be as exciting and gratifying as getting a research article published in a scientific journal. In this quest, I selected Diazepam (Valium, an antianxiety agent produced by Roche) as its sales were growing significantly globally while its production was only in kilo gram quantities per annum. The process that was patented by Roche was tedious for the Indian manufacturers to scale-up. The original Roche process made the key intermediate – "2-methylamino-5-chlorobenzophenone" starting from 4-chloroaniline by reacting with benzoyl chloride in molten zinc chloride and the resultant product was subjected to acid hydrolysis to yield 2-amino-5-chlorobenzophenone. This was then subjected to N-methylation using a classical method and finally converted to Diazepam. I developed a simple process whereby the

Dr. Yusuf K Hamied

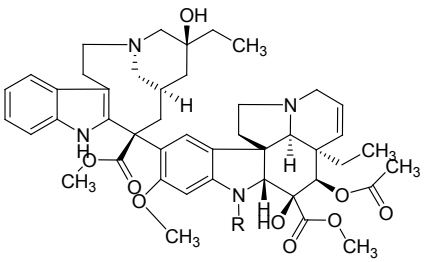
CSIR-Indian Institute of Chemical Technology

same intermediate could be made starting from 4-nitrochlorobenzene using simple operations which made the product drastically cheaper compared to the original patented process. In 1973, I met Dr. Y K Hamied, who was then the Director of R&D in CIPLA and informed him about my work on Diazepam. He was so impressed with my approach that he decided to buy the route of synthesis without waiting for our process scale up. He met Dr. Tilak and told him that he would like to make a one-time payment on nonexclusive basis for the laboratory process developed by Rama Rao. This was the first drug process technology sale from CSIR-NCL that was successfully commercialized by an Indian industry.

Rama Rao's Contributions to Indian Drug Industry - Consultancy and contract research:

After my return from Harvard University working in Prof. E J Corey's group, it was my intention to continue working on important industrial projects. The isolation of Vinblastine and Vincristine, two complex alkaloid molecules from Madagascar periwinkle - *Vinca Rosea* leaves seemed like a colossal challenge to take on. *Vinca Rosea* (*Catharanthus roseus)* was widely grown in India and known for its medicinal properties. In fact, even today some people in Kerala use the dry leaf decoction believing that it cures diabetes. In late 1950's, a delegation from Eli Lilly came to India to look at the Indian medical system and the plant materials that were used as herbal remedies. They carried with them the Vinca dried leaves and looked for antidiabetic agents from the leaf extract. They could not find any active component for the treatment of diabetes but were surprised to realize that the extract contained an anticancer agent. The plant contains nearly 95 alkaloids which were mostly monomers but a small fraction of the alkaloids were dimeric. The Eli Lily team separated the active vinca-alkaloid named Vinblastine using a very tedious alumina column chromatography. Further, they also isolated another minor component named Vincristine which was more active and an effective treatment for pediatric leukemia. Based on these positive results they were importing huge quantities of dried vinca leaves from India. With the growing demand some of the traders who were exporting dried vinca leaves became greedy and started adulterating the vinca leaves. Faced with this problem of getting good quality raw material from India, Eli Lilly started their own plantations near Houston in the southern parts of US where the climate was suitable to grow the Madagascar periwinkle plants. Around the early 1970's, sourcing of the leaves from India was stopped. This led to a political problem with the Maharashtra government having to deal with livelihood of many people who were growing and harvesting this medicinal crop. The state government started procuring these dried leaves and were keenly looking for an institution to develop an indigenous approach to isolate the two valuable dimeric alkaloids. In 1978, I approached the Maharashtra Government for funding to take up this project and was given a grant. My research group quickly worked out a simple process of isolating vinblastine using a solvent extract technique from the vinca dried leaves thereby totally avoiding the tedious chromatography column separation. We then converted it by a simple potassium permanganate oxidation to give Vincristine. We also worked out a way to formulate the drug substance by way of lyophilizing in the form of vials with the help of Hindustan Antibiotics Limited (HAL). For the first time, we demonstrated that the bioavailability of the drug was identical with Eli Lilly's imported vials with assistance from the Head of the Chemotherapy at the Tata Cancer Hospital, Mumbai. The entire technology including its formulation process was passed on to Cipla for commercialization. Cipla introduced both these two natural anticancer agents in 1983 in India and subsequently in 1985 started exporting these two compounds to US and Europe. This was the second example of successfully achieving a solution to a difficult problem where better technology was developed in NCL and commercialized by a domestic company.

Another example which came out from the National Chemical Laboratory was Vitamin-B6. The work on Vitamin-B6 was initiated at NCL in 1958 based on the directive from the Government of India to work on an indigenous process technology and pass it on to the Indian Drugs and Pharmaceuticals Limited (IDPL) in Hyderabad for commercialization. NCL started working on the original twelve step process based on Harris and Folkers method of Merck. When NCL scientists initiated the work in 1958 the cost of vitamin-B6 in international market was 450 USD per kilo but by 1963 the price came down to 80 USD per kilo. This dramatic change happened based on a publication by Kondratyers from USSR stating that substituted hydroxypyridines could be made by a simple Diels Alder reaction involving substituted oxazole with dimethyl acetylene dicarboxylate. Pursuing this new finding, the project was once again taken up by NCL based on Merck process and carried out on pilot plant scale by 1973. But by then the price of vitamin-B6 came down to 30 USD, which the NCL process was not able to meet, and the project was shelved. Later, when I took over as the Head of the Organic Chemistry Department in 1980 at NCL and I was keen to revive the process to work on the vitamin-B6 despite the then Director's reluctance. We realized what went wrong with the earlier process. They used 4-Methy-5-ehtoxyoxazole as the diene, which is very unstable to heat and resulted in lower yields after Diels Alder reaction. Contrary to it, we used 4-methyl-5-cyanooxazole as the diene, which is relatively stable to heat and reacted with cis-1,4-butene diol acetonide as the dienophile. By this way, the process worked out better, successfully carried out on pilot scale and finally commercialized by Lupin Laboratories in their Ankleswar unit in 1985. I continued to associate with Indian industries and taken up several projects under sponsorship or what is referred to as contract research today. I was also an active consultant with several Indian pharmaceutical companies. We worked on developing processes for beta-blockers such as Atenolol and Metoprolol for Cipla and for the first time in India made a chiral drug - Timolol and passed on its technology to FDC, Bombay.



Vinblastine: R=Me
Vincristine: R=CHO

Subsequently, I moved to Hyderabad as Director, Regional Research Laboratories (RRL) in 1985 which was renamed as the Indian Institute of Chemical Technology (IICT) in 1988. Here, I continued to work closely with Indian pharma industry. At IICT, we developed technology for making an anticancer drug, Etoposide and successful transferred the technology to Cipla for its manufacture. We also developed a laboratory process for Norfloxacin and Ciprofloxacin for Cipla. We were also instrumental in developing several other processes for Indian pharma which include Flurbiprofen (for FDC), Astemizole and Gemfibrozil (for Cadila), Mefloquine and Sulbactam (for Unichem).

Indian Pharma Revolution after 1972:

Many Indian companies were very keen to take advantage of the new 1972 patent law in India and started copying some of the new and essential drugs which were being made internationally and were keen to introduce them in Indian market. The demand for talented chemists and chemical engineers spiked as more R&D and production units were established. Several entrepreneurs with technical expertise ventured into starting their own companies. One such successful example was Dr. K Anji Reddy, a graduate in chemical technology from UDCT and obtained his Ph.D. in chemical engineering from NCL and joined IDPL as technical officer in 1968.

He was directly involved in taking up R&D projects of IDPL, scaling up on pilot plant and manufacturing. He was very keen to go on his own and set up a company - Uniloids with two other partners in 1974. They started producing Metronidazole which became a big hit in the Indian market. Later he parted ways and founded Standard Organics Limited in 1980 to manufacture Sulfamethoxazole and Trimethoprim. Standard Organics quickly became the leader in the domestic market for these two drugs and also started exporting them to other countries. Anji Reddy started another company named Cheminor in 1981 with Mr. Murali Divi to exclusively manufacture Ibuprofen. Anji Reddy was a family friend, both at UDCT and subsequently at NCL before he left for Hyderabad to work at IDPL. He consulted with me to know more about the Ibuprofen process which we had developed and transferred to Cipla on a non-exclusive basis. I had some new ideas and suggested to use a process starting from 4-isobutylacetophenone, reducing the ketone to alcohol,

Dr. Kallam Anji Reddy
(1939 – 2013)

Dr Reddy's grew into a multinational and today has revenue around USD 2.5 billion manufacturing over 60 API's and is the fifth largest pharma company in India.

The city of Hyderabad continued to produce many great pharma entrepreneurs and is home to majority of the country's top pharmaceutical companies. Aurobindo was founded in 1986 by Mr. P V Ramprasad Reddy; Divi's Laboratories founded in 1990 by Murali Divi; Hetero Drugs founded Dr. B Parthasaradhi Reddy in 1993. All above three were colleagues and associates of Dr. Anji Reddy.

Today, Hyderabad accounts for 40% of total Indian bulk drug production and 50% of them are exported and is regarded as a "Bulk Drug Capital of India".

Cipla was founded by Dr. K A Hamied in 1935 and in the beginning the company confined to formulations and did not manufacture drugs. In 1960, his eldest son Dr. Yusuf K Hamied completed his Ph.D. in chemistry from Cambridge University joined Cipla as its R&D Head. He realized that Cipla would not grow unless it has its own drug manufacturing facilities. Cipla was the first company to introduce steroids in the country and later went on to manufacture almost all the major generic drugs and their formulations. Having had the training in synthetic organic chemistry, Dr. Yusuf Hamied also pioneered the concept of academic and industry interaction and sponsored several projects with my research group at NCL and subsequently at IICT. In 1991, I approached him to commercialize Zidovudine, commonly known as AZT, which at that time

Inaugural function of Cipla Patalganga factory in 1984 (from Right – Dr. A V Rama Rao, Dr. Y K Hamied, Dr. G S Sidhu, DG-CSIR, Hamied's Mother)

was the only drug available for treating HIV and AIDS patients. Initially he was reluctant to introduce this drug as he felt the market was limited. I convinced him that HIV would soon be a major problem in India. Further, I pleaded with the Government of India to waive the import duty on the starting material Beta-Thymidine to help lower the cost of the drug production. I also impressed on the Drug Controller of India on the importance of AZT production by Cipla to facilitate clinical trials to the extent possible within the country. By the combined efforts of the Government and my research group, Cipla commercialized the AZT production in 1993 and marketed the 100 mg capsule formulation at 1/6th of the then prevailing international price. Later Cipla developed several anti-HIV medications and offered the world's first triple single drug cocktail named Triomune at a price of less than one USD per patient per day. Being HIV positive is no longer a death sentence and can be treated as a chronic disease with affordable medicines, thanks to Cipla and several Indian companies that are manufacturing these drugs at low cost.

Future of Indian Drug Industry:

In 1994, India joined the World Trade Organization and accepted the TRIPS mandate. The Indian Patent Act of 1972 was amended on 26th December 2004 and came into effect from January 2005. By this act all product patents were allowed in all sectors, license of right deleted, it also allowed micro-organisms to be made patentable while the pre and post grant opposition provision was included in the act. The Government can sanction compulsory licensing wherever required for domestic use. The Indian patent act of 2005 specifically stated that incremental changes will not be regarded as exclusive right. Based on this analogy, drug controller of India did not allow its product patent for Novartis for Imatinib. They appealed to supreme court, even then the court ruled that it was an improved version and not a new invention. India also issued its first compulsory licensing in March 2012 to NATCO Pharma to manufacture Bayer anticancer drug "Nexaver".

After the new patent law, Indian companies invested large sums of money for drug discovery. Dr. K Anji Reddy founder of Dr. Reddy's was a pioneer and made huge investments in the search for new drugs in therapeutic areas such as antidiabetic, cardiovascular and analgesics. These efforts led to development of the two antidiabetic drug candidates which were taken up by multinational companies for further clinical trials. Unfortunately, as is the case with several drug candidates, they could not provide the required results to make it to market.

So far there is only one indigenous drug in the Indian market and this was developed by the Central Drug Research Institute (CDRI), Lucknow. Thanks to the efforts of its former Director, Dr. Nitya Anand, the compound known as Centchroman (Generic name – Ormeloxifene) was introduced in India in 1991 and is a nonsteroidal oral contraceptive. The drug is marketed under the trade name Saheli by Hindustan Latex Limited and used by many women as an oral contraceptive taken one pill per week. This drug is distributed free of cost through government hospitals.

The present global API market is around USD 200 billion while the global pharmaceutical market is valued at USD 1.4 trillion. While these numbers appear attractive, the business itself is very competitive with more than 2000 firms and 5000 manufacturing sites. Currently, India has a reputation in producing high quality and low-cost generic drugs in the world. This industry has been valued at USD 42 billion by 2020. India is the third largest provider of generic medicines by volume and having 20% of global market share. It is also the largest supplier of vaccines to the world by volume and accounting for more than 50% of all vaccines manufacturing in the world. Indian pharmaceutical business is showing an annual average growth of 11% per annum and is expected to reach 60 billion USD in value by 2024. The future of the pharmaceutical business in India is promising and investments into this sector are only increasing, but the area of concern where India needs to achieve self-sufficiency is in the production of raw materials used for making APIs. Most of the Indian companies depend on the import of key starting materials from China and this accounts to 58% by value and 80% by volume. Most of the fermentation products especially antibiotics and almost all steroids are being imported into India from China. Although India is known as the largest producer of Metformin in the world which is used for treating diabetes; two key intermediates for making this drug are imported from China. To counter this dependence on China, in recent years, the Indian government came out with incentives to be given to domestic companies that can produce products without the need for any raw materials being imported.

For the last two decades several entrepreneurs have entered the pharmaceutical business with start-ups offering a gamut of research services along with testing and manufacturing capabilities. I was one of the early entrants who believed in the contract research as a business story. After my retirement at the age of 60 as the Director of CSIR-Indian Institute of Chemical Technology (IICT) in 1995, I started my own venture named Avra Laboratories Private Limited to offer R&D services to multinational companies. Avra grew quickly and built a reputation for being able to work on complex problems and offer low-cost solutions. Our success led many other companies to take notice of the opportunities and join in this space of contract research and manufacturing.

Dr. Nitya Anand

Within a span of a decade, India became a preferred destination for global pharmaceutical companies to source both products and research services. Besides succeeding as a contract research organization, Avra became the first company to produce a complex anticancer drug Irinotecan by total synthesis. Originally, this drug was made from a starting compound Camptothecin, a natural plant alkaloid which has the complex core and is converted to Irinotecan through a semisynthetic approach. Today Avra is a global leader offering advanced intermediates that allow for the facile production of Camptothecin related derivatives.

Dyes & Pigments - Introduction:

Human beings always use colours to decorate themselves, garments, tools, and their surroundings for beautification. Traditionally colours were derived from natural sources. India was known for centuries for producing natural colours derived from plants or insects to dye fabrics. Even during the bronze-age civilization of Mohenjo-Daro, there is evidence of the use of natural colours being applied to fabrics, pottery, and other items. Archaeological data shows evidence of dyeing fabrics with colours derived from plants and insects traced back to about 5000 years in places from the Fertile Crescent, a region in the Middle East considered the cradle of civilization and China.

Natural dyes are derived from plants, invertebrates, or minerals. While most colouring agents are of plant origin others are obtained from biological sources such as insects and fungi. Many natural dyes require the use of chemical compounds called mordents to fix the dye to the fabrics. Mordents are normally inorganic salts such as alum, Ferric sulphate, copper sulphate and other polyvalent metal ions that form a coordination complex with dye and attach to the fabric. Examples of such traditional natural dyes include Tyrion, Crimson, Kermes, Indigo, Saffron, and Madder.

Till the end of the 18th century, Indigo was much sought after from the blue colour it imparts to the fabric. The oldest indigo coloured fabric was discovered in Peru and dates to around 6000 years ago. India was a major center for its production and processing where the plant was cultivated in Bengal.

Cutch is another Asian dye from the wood of Acacia tree, commonly found in India for dyeing cotton to give green, brown colours using an iron-based mordent and an olive brown colour when used with copper salts. Turkey red used for dyeing cotton and was isolated from madder root of the Rubia plant, a process that was developed in India and spread to Turkey. Indian Madder (Rubia cordifolia) is found in the Himalayan regions and still used by craft dyers in Nepal. Besides the spice trade, it was these dyes that brought the Europeans and the East India Company to trade and later colonize parts of India and Asia.

Lac dye is the colouring matter of the lac resin produced by the insect Kerria lacca. The structure of Lac dye eluded the scientists more than five decades after its isolation. The dye known as laccaic acid was first isolated in 1887 and regarded as a single compound. However, efforts to obtain pure laccaic acid eluded scientists for a long time. Renowned Indian chemists, Prof. K Venkataraman, and Prof. T R Sheshadri dedicated a lot of time and effort to identify to its structure and see whether a synthetic alternative could be commercially produced. Prof. K Venkataraman's group spent more than 10 years between 1955 to 1965 and could not elucidate its structure. However, they demonstrated that the dye was a mixture of at least two compounds, one of them having an aliphatic nitrogen in the form of an amine present as the major component. In 1965, I was appointed as a scientist in Venkataraman's group, and he assigned me the task to continue the search for the structure of lac dye. As I worked on this project, I found that the compound was a mixture of two major compounds, one containing a nitrogen as was anticipated along with two more minor components that were named laccaic acid D and laccaic acid E. We were able to determine all the structures based on NMR and mass spectral data. We learnt that one component was missing in the lac dye referred as laccaic acid C derived from tyrosine. We also established a biogenetic synthesis starting from laccaic acid D coupling with tyrosine to yield laccaic acid C, decarboxylation gave laccaic acid E which on acetylation of the amino group gave the major laccaic acid A with its distinct red colour. The pure lac dye was found to be totally non-toxic and could be used as a food colouring agent. Unfortunately, the purification cost is very expensive, and the costs prohibited its use in pure form. In the past the natural resin was used to make gramophone records and telephone equipment, today, its resin is used as a commodity by the paint industry.

The Advent of Synthetic dyes:

The first synthetic dye, Mauve was discovered by W H Parkin while carrying his Ph.D. program to synthesize quinine at the age of 18 years. The compound was bright red and dyed fabric which was not washable. He filed a patent in August 1856 and established the first factory to manufacture synthetic dyes in Greenford, near London. He became rich at a very young age. After this, many major chemical industries such as BASF and Bayer in Germany started working on synthetic dyes in a major way. Indigo which was a most important natural dye from India was first synthesized by Adolf Von Baeyer who reported its synthesis in 1878 and commercialized its manufacturing in 1890. Baeyer received the Nobel prize in chemistry in 1905 for his contribution to the synthesis of Indigo. The synthetic indigo replaced the natural product in 1914 and only 4.1% of the total production of natural dyes came from plants.

The first synthetic dye was made in 1856 and in subsequent years several different classes of dyes entered the market and last class of reactive dyes came from UK from ICI in 1956. Dyes are classified by their method of application to a substrate and placed in categories such as direct dyes, reactive dyes, vat dyes, disperse dyes, azoic dyes, and other types.

Most of the dyes were manufactured using big reactors by utilizing batch operations. With time several improvements were made in the production of synthetic dyes in the form of workup, drying using agitated thin film dryers, and falling film evaporators. Much of the research work was focused on the dye application on cotton, polyester, and polyamide fabrics. Efforts were also made to achieve very high fixations using reactive dyes on cotton and leather, to reduce dye discharges from entering into effluent streams.

Indian Dye Stuff Industry:

The first dye stuff industry unit in India was the Associated Research Laboratories now called ARLab, established in 1941 near Pune, the next big facility in the organized

sector was set up by Atul Industries in 1947 in Bulsar where a variety of dyes were produced from 1957. Indian textile industry, which was originally using natural dyes, now totally switched over to synthetic dyes. Two well-known industries in Mumbai in the years between 1960 – 1980, were Amar Dye Limited and the Indian Dyes Industries (IDI). Along with Atic (Atul in collaboration with ICI), was the largest dyestuff industry meeting most of the Indian demand.

The Indian dyes and pigment industries have contributed significantly to the overall growth of the Indian chemical industry. Approximately Rs. 48,000 crores (USD 60 billion) was generated by this industry in the year 2022. This is still a growing sector creating jobs and contributing to exports from India.

In India the top 50 manufacturers of dyes and intermediates have nearly 65% of the total dyestuff market share, the rest of the 35% come from the unorganized sector of small and medium industries of more than several thousand units.

Among the synthetic dyes, the reactive dyes are much in use with a production capacity of around 100,000 tons. For direct dyes the production quantities are nearly 20,000 tons, while disperse dyes, basic, sulphur, and others have a capacity of approximately 10,000 tons per annum. These dye stuffs find several applications in industries where 80% of the dyes are consumed by the textile industry. The growth of the textile and leather industries is a consequence or supplement for the growth of dye industry. In India, nearly 90% of dye stuff manufacturing confined to Gujarat and Maharashtra states. In the year 2017 India exported dyes worth approximately 2.4 billion USD. Among them US constitute 8%, Turkey 7.1%, Bangladesh 6%, China 5.7%, Germany 4.6%, Italy 4.3%, Brazil, 3.9% and rest for other countries.

Although organic chemistry as a subject was popular and research labs were started in most Indian institutions and universities, not much attention was given to the chemistry of dyes. There was only one institute in the country, the Institute of Chemical Technology (ICT) in Mumbai which carried out research devoted to textiles chemistry as well as dyes right from its inception in 1934 and now has the Department of Fibres and Textile Processing Technology.

The first Indian Director of the University Department of Chemical Technology (presently ICT) was Prof. K Venkataraman, he was an expert on synthetic dyes and also the first academic to write two volumes on synthetic dyes and their intermediates in 1952. These two volumes were the main source of information related to the dye stuff technology and were so popular that they were translated into 13 international languages.

Pigments:

Pigments are also colouring matter and different from dyes. Pigments are not soluble in solvents, that they can only be suspended in a medium with the help of a binder, on the contrary dyes are substances that go into solution and can impart colour to the fabric. There are two types of pigments where most of them are inorganic pigments while the rest are organic pigments. Inorganic pigments consist of minerals and metal content that imparts their colour and are primarily based on oxide, hydroxide, silicate, sulphate and carbonate types and classified into four groups: white pigments, black pigments, coloured pigments and specialty pigments. They are manufactured by a simple process involving operations such as washing, drying, powdering, sieving and finally formulating.

Organic pigments are also natural products which change the colour of reflected light because of wavelength-selection absorption. Carotenoids are pigments in plants that produce as variety of red to yellow colours as they absorb violet to green light. The red colour of roses is due to pigments that absorb all colours of normal visible light except red which is reflected giving the rose its red colour. The leaves of plants are green due to the pigment chlorophyl, while the colour of our skin is due to the pigment melamine.

Synthetic pigments are compounds that are made in the laboratory and produced on a commercial scale with a greater control over their production. These pigments are widely used in paints, polymers, synthetic fibers, ink and more recently in electronic devices. A good pigment has the following properties: they mix freely, they show chemical resistance, they are normally brilliant and show resistance to light, wetness, and abrasion. In addition, their particle size range is between 0.2 to 0.4 and have an excellent dispersion property and because of scientific advances in field of synthetic pigments several shades of pigment are available for a variety of uses. The red colour of the Ferrari car is from a pigment based on an organic compound called DPP (diketopyrrolopyrrole) which was first synthesized in 1974 by Donald G Farnum at Michigan State University. Pigment Red 254 aka Ferrari Red was developed and patented by Ciba-Geigy in 1983.

In India dyes and pigments are made by several manufacturers. Among the major dyes and pigments manufacturers in India include: Poddar Pigments, Priya Limited, Sadhana Nitro, Sudharshan Chemicals, Sree Hari Chemicals, Ultramarine, Vidhi Dyes, Vipul Organics and others.

Agrochemicals- Introduction:

In the year 1960, as I started my career as a research fellow at the National Chemical Laboratory (NCL), Pune, working for my Ph.D. degree. Growing up in India, we were familiar with droughts, food shortages and famines in the country. Around that time, Norman Borlaug had become famous for his success in growing high yielding wheat strains in Mexico. Renowned Indian Geneticist, M S Swaminathan wrote a letter to the Director of the Indian Agricultural Research Institute that they should invite Norman Borlaug to learn more about his techniques and if they could be applicable in India. In 1963 Dr. Borlaug visited India and brought with him four promising strains of wheat that were planted in Northern India. These seeds worked perfectly in the Indian climate and were also resistant to rust. A report in the New York Times notes, "In pre-Borlaug 1963, wheat grew there (in India) in sparse, irregular strands, was harvested by hand, and was susceptible to rust disease. The maximum yield was 800 lb per acre. By 1968, thanks to Borlaug's varieties, the wheat grew densely packed, was resistant to rust, and the maximum yield had risen to 6,000 lb per acre.". It was also during this time, India adopted IR-8, a semi-dwarf rice variety developed by the International Rice Research Institute. Soon the yield of wheat and paddy in the country went up to 5 to 6 times higher per hector. A green revolution had begun in the country. This dramatic increase in wheat and rice production was attributed to new strain of seeds along with the use of fertilizers to promote plant growth, and pesticides for crop protection which was coupled with better irrigation facilities. India was on the path towards self-sufficiency in its food production and in the subsequent years it became a major exporter. Norman Borlaug was awarded Nobel Peace Prize in 1970. Prof. M S Swaminathan was responsible for this transformation and is regarded as the father of Indian green revolution.

In recent years, India's need for food grains is growing steadily due to increase in population (1.3 billion people) and at the same time there is constant decline of the cultivable land as much is lost to growing cities with expanding infrastructure for living and industry. For this reason, the Government of India is being forced to enhance farming methods by the use of fertilizers and crop protecting agents.

The history of Indian fertilizer industry:

Back in 1906, the first fertilizer factory in India was opened at Ranipet (Tamil Nadu). In terms of the scale of investment, the fertilizer industry is regarded next to steel. The present global fertilizer market size is around USD 190 billion and there was a 12% growth from the previous year. also is expected to reach double the requirement. Fertilizers are essential for food security. With the available limited land, farmers must use fertilizers to enhance the nutrients in the soil that were taken up by previous crops.

The top 3 Indian fertilizer companies have a market size of around 57% with Chambal Fertilizers and Chemicals Limited Coromandel International Limited leading and having an installed capacity of 1.5 million tons per annum (MTPA). The state of Gujarat is the top producer of fertilizers, while Pondicherry tops the consumption (in kilos per hector) followed by Telangana and Punjab.

Pesticide industry in India:

Pesticides are compounds used as crop protecting agents and include insecticides, herbicides, rodenticides, and fungicides. 292 pesticides are registered in India and of these 40% are organochlorines. Rice has the highest rate of pesticide usage (29%) followed by cotton (27%), vegetables (9%) and pulses (9%). In India, there are about 125 technical grade manufacturers including 10 multinational companies and 800 formulators with several distributors. The formulations are made from technical grade active ingredients by adding inert carriers, adjuvants, emulsions, solvents, and surface-active agents. The Indian agrochemical market is challenging and suffers from high inventory and long credit periods to farmers, thereby, it requires huge working capital. However, its strength comes from low cost manufacturing and qualified personal making India is the 4th largest exporter of pesticides in the world after China, USA, and France.

The main pesticide manufacturers in India include United Phosphorus Limited (UPL), BASF, PI Industries, Bayer Crop Sciences, Syngenta India, and Rallis India where the top ten companies control almost 80% of the market share. These large players have an extended product portfolio and are regularly introducing new molecules. New global strategic alliances and acquisitions are allowing for greater global reach increasing their market share.

In recent years, the Indian government has been advocating integrated pest management and there is also a demand for organic farming. In addition, the spurious pesticide market in the country is growing steadily along with improper use which impacts the revenue and reputation of the organized sector.

Indian Institutions and Industry Interaction:

After the abolition of the Indian product patent laws in 1972, The government of India directed CSIR laboratories to work on processes for both drugs and agrochemicals. The National Chemical Laboratory (NCL), Pune and the Indian Institute of Chemical Technology (IICT), Hyderabad, initiated technology development programs, performed pilot scale studies and finally helped design chemical plants for pesticide production. NCL worked out on Endosulfan and commercialized the product by transferring technology to industries. IICT initiated a major program on organophosphate pesticides such as Monocrotophos, Chlorpyriphos, Cyhalothrin (pyrethroid) insecticides, and Butachlor herbicides. Chlorpyriphos was much in demand and IICT prepared plant designs to enable the production of 300-400 tons per annum and the technology was transferred to over a dozen Indian companies. In addition, we worked on. IICT also carried out work on developing Neem based biopesticides having Azadiractine (13%) for commercial production. IICT was also involved in developing technology for promoting the use of biopesticide - Bacillus thuringiensis, a soil dwelling bacterium and its spores and insecticidal proteins are used in pest control.

Exports:

The global agrochemical market was around USD 225 billion in 2021 and is projected to reach USD 300 billion by 2030. The Indian agrochemical industries valued at around USD 5.72 billion USD in 2020-2021, with domestic consumption around USD 2.72 billion and exports at USD 3 billion. The forecast was exports is growing and many Indian companies like United Phosphorous, Gharda Chemicals, Excel industries and PI are now increasing their global footprint.

A vast majority of the pesticides that are being used are formulations of generics – products whose patent life has expired. Generic pesticides account for 60% of the global crop protection market. In the next ten years (2021-2030) around 22 patented pesticide compounds will become generic. These are Bixafen, Chlorantraniliprole, Cyantraniliprole, Fenpyrazamine, Flubendiamide, Fluopicolide, Fluopyram, Fluxapyroxad, Isopyrazam, Mandipropamid, Penflufen, Penthiopyrad, Pinoxaden, Pyriofenone, Pyroxsulam, Sedaxane, Thiencarbazone-methyl, Valifenalate, Benzovindiflupyr, Sulfoxaflor, Saflufenacil, and Aminopyralid. This would create a 3 to 5 billion USD opportunity for generic manufactures.

Bhopal Gas Tragedy was considered as the world's worst industrial disaster due to a pesticide industry in India purely by not implementing safety measures and the negligence of the work force.

References

1. Hamied, Y.K., Indian Pharma Industry: Decades of struggle and achievements. 2nd April 2005 Lecture at IICT, Hyderabad
2. Rama Rao, A.V., Vishwakarma Medal Lecture – 1991, Proc. Indian Natn. Sci. Acad. 58, 1992: 287-311
3. Generic Drugs – Saving lives with Generosity, Kavita Tiwari – Indian Science Transforming India, A look back on its 70-year Journey
   Indian National Science Academy – 2018
4. Indian Drugs and Pharmaceuticals Limited
   https://www.idplindia.in
5. Annual report 2020-21 – Department of Pharmaceuticals, Government of India
   https://www.pharmaceuticals.govt.in
6. Global Dyes Market outlook 2018-2022, Robust Growth
   https://www.prnewswire.com, 14th February 2019
7. Dyes and Pigment market size, Global Intelligence Report
   https://www.globenewswire.com, 08th October 2021
8. Rama Rao A.V., Venkataraman K., Insect pigments derived from hydroxyanthraquinones
   Recent Development in the chemistry of Natural Products. Prentice – Hall of India Pvt. Ltd., New Delhi, 1972
9. Agrochemicals and their importance in Agriculture
   https://www.researchdive.com
10. Indian Organic Chemical Industry: Decades of Struggle and Achievements
    A V Rama Rao, Indian Journal of History of Science, 49, 399 (2014)