Chapter I

Introduction: History of Indian Pharmaceutical Industry: Requirement of Process Development

Indian pharmaceutical history began from Gupta period which was existed from approximately 320 to 550 CE. Charak Samhita and Sushruta Samhita are the two foundational texts of Ayurvedic therapy having critique on medicine, pharmaceutics and surgery. Indians were dependent only on the indigenous form of medicine before British rule. The use of this therapy is still being studied and used not only in India alone but also in rest of the world.

In India Allopathic medication was started in British rule. But production of such medicines was not in the country. Foreign countries use to make the final products in their units using the raw materials imported from India and exported those medicines to India again. It was 1982 when few of the Indian scientists like P C Ray, T K Gajjr, and A S Kotibhaskar laid a foundation for a pharmaceutical industry. In 1901 Acharya P C Ray started first Indian Pharmaceutical Industry, Bangal Chemical in Calcutta. Within few years some more Indian entrepreneurs came forward to form the pharmaceutical industries. In 1907 Alembic Chemical Works in Baroda, in 1919 Bengal Immunity were started. This was considered as a foundation of Indian pharmaceutical industry. This initial achievement of drug industry could meet 13% of countries medicinal requirement. During the Second World War (1939-1945) there was a huge fall in supply of drugs from foreign companies. As a need number of pharmaceutical companies started in India. This includes Unichem, Chemo Pharmaceuticals, Zandu Pharmaceutical work, Calcutta Chemicals, Standard Chemicals, Chemical Industrial and Pharmaceutical Laboratories (Cipla), East India Pharmaceutical Works etc. With the establishment of such new pharmaceutical industries before independence, almost 70% of the countries requirement was achieved.

From 1950s global pharmaceutical sector observed a tremendous growth. Numerous new drugs were developed and produced on scale. These included the first oral contraceptive, "The Pill", Cortisone, blood-pressure drugs and other heart medications. MAO Inhibitors, chlorpromazine (Thorazine), Haldol (Haloperidol) and the tranquilizers
ushered in the age of psychiatric medication. Valium (diazepam), discovered in 1960, was marketed from 1963 and rapidly became the most prescribed drug in history, prior to controversy over dependency and habituation. The countries like Germany, Switzerland, UK and some extent US are the major countries contributed for the global growth. A systematic approach in medicine was started that include treating the symptoms to treating the diseases itself. Industries were focused on research and development rather in building more and more production units as the industry observed invention and commercialization the newly invented drugs like Penicillin and other synthetic drugs.

On the other hand the Indian pharmaceutical sector was not a part of the global revolution. The capital, new technologies were major factors affected on the growth of Indian sector. It was recognized that participation of foreign capital and enterprise, particularly as regards industrial technique and knowledge, will be of value to the rapid industrialization of the country. Hence government of India tried to attract multinational companies to invest in India. As a result of liberalizations in government policies, many foreign companies invested in Indian sector. With the government efforts and investment of global entrepreneurs, Indian pharmaceutical sector could achieve the growth of Rs 35 crore in 1952 from Rs 10 crore in 1947.

This growth was mainly contributed by manufacturing the bulk drugs rather than final product. When Government of India observed that in the pharmaceutical sector the multinational companies (MNCs) were behaving just like trade agents, i.e. importing drugs and marketing in India and were not engaged in activities that would build domestic competence, a new strategy with the lead role assigned to the public sector firms was devised for building up the pharmaceutical industry. The Industrial Policy Resolution of 1956 classified industries into three categories based on their priorities. “Schedule A” industries were exclusively reserved for the public sector and “Schedule B” consisted of industries, where the public sector would play a lead role and the private sector was expected to supplement the efforts of the State. “Schedule C” consisted of the remaining industries whose future development was left to the private initiatives. The pharmaceutical industry fell under Schedule B. Private industry was also encouraged, though strictly regulated through industrial licensing. In the licensing policy, government
made it mandatory for the multinational units to produce the final drug in their units from the basic stage. The licensing was granted under the supervision of The Directorate General of Technical Development for setting up the new units or expansion of the existing units keeping into an account of the medicinal need of the country.

As a result of this policy many MNCs expanded their units and many new Indian companies established. With this the Indian pharmaceutical sector could achieve the growth up to Rs 100 crore in 1962.

In pursuit of these policies, the Government of India established five public sector companies in India of which two played very important roles- Hindustan Antibiotics Ltd. (HAL) and Indian Drugs and Pharmaceuticals Ltd (IDPL) in 1954 and 1961 respectively. IDPL was established in with technical assistance from USSR and HAL with the technical assistance of World Health Organisation (WHO) and United Nations International Children’s Emergency Fund (UNICEF). The two companies played a major role in building up technical competence in the industry as well in establishing a strong bulk drug industry in the country.

HAL is the first drug manufacturing company to be set up in the public sector by government of India with the social objective of providing affordable drugs throughout the country. Initially it was started with manufacturing Penicillin. It is the first company in India to commence bulk production of Streptomycin sulphate, Penicillin-G, 6-APA and Ampicillin. It is only Indian company in pharmaceutical segment to discover two new molecules namely Hamycin and Aurofungin.

The two companies played a major role in building up technical competence in the industry as well in establishing a strong bulk drug industry in the country. IDPL and HAL created a new environment and confidence that India could manufacture bulk drugs in a major way. The university system in India at that time did not provide the specialized training required by the pharmaceutical industry. IDPL and HAL not only encouraged the university system to impart specialized training required for the pharmaceutical industry by creating a demand for skilled labor but also sparked industrial developed in upstream and downstream business by generating demand for specialized capital and other
services. It was this dynamism that led to the creation of a bulk drug manufacturing industry in Hyderabad where the synthetic drug plant of IDPL is located.

IDPL started its three units in the country with main objective of creating self sufficiency in respect of essential life saving medicines to free the country from dependency on imports and to provide medicines to the millions at affordable price and not to make millions from the medicines. IDPL was basically conceived and established as a part of health care infrastructure and has played a pioneering infrastructural role in the growth of Indian drug industry base.

These two companies also made considerable efforts in the adaptation and assimilation of technologies supplied by their sponsors to meet Indian requirements. Modifications were required due to technological imperfection and due to the physical and economic climate in which the technology was being implemented. Efforts were also made for the exchange of technologies between the two firms. The government insisted that the technologies developed in the laboratories of IDPL and HAL from time to time, be shared with each other. When it was found that the technology agreements with their sponsors were prohibiting the transfer of technologies between the two firms, the government found a way out by making scientists from each company work in the other. When Merck & Co. of United States (US), which provided the technology to the streptomycin unit of HAL, objected to the sharing of the technology with IDPL and the USSR strongly objected to the application of technology of Merck & Co. in IDPL, the Government appointed a senior technologist of HAL to work in IDPL’s antibiotics plant. The technologies available in these firms were spilled over to the private sector by way of movement of scientists and technicians from public sector companies to the private sector. Some of the founders of private sector bulk drug manufacturing companies had earlier worked in public sector or companies, for example Dr. Anji Reddy, the founder of Dr. Reddy’s Laboratories, had worked in IDPL.

In 1911, the Government of India set up the Indian Research Fund Association (IRFA) with the specific objective of sponsoring and coordinating medical research in the country. After independence, several important changes were made in the organization and the activities of the IRFA. It was re-designated the Indian Council of Medical
Research (ICMR) in 1949, with considerably expanded scope of functions. ICMR, the apex body in India for formulation, coordination and promotion of biomedical research is one of the oldest medical research bodies in the world.

Council of Scientific and Industrial research was established in 1942 with the mission to provide scientific industrial research and development that maximizes the economic, environmental and societal benefits for the people of India.

Central Drug Research Institute (CDRI), Indian Institute of Chemical Technology (IICT) and National Chemical Laboratory (NCL) are among the few research institutes guided by CSIR and ICMR. These institutes contributed considerably for the growth of Indian pharmaceutical sector. The processes developed by such institutes were well transferred to the private units for the scaling up the product. Number of technologies were developed and successfully commercialized. Many Indian pharmaceutical industries including top most companies were benefited from the services provided by these research institutes.

In 1970s the growth of Indian pharmaceutical sector increased up to Rs 72 crore for bulk drug and Rs 370 crore for formulation. Still the Indian pharmaceutical companies were not gaining much as the share of MNCs was more with high value products taking the advantage of Product Patent in Patent act of 1911 where as significant units from public and private entrepreneurs were immerged in the same period lowering the cost of bulk drugs. To overcome these differences government of India with its own experience and with the recommendation of number of existing entrepreneurs changed the policy and Process Patent came in to existence with reduction in the life of the patent. Indian pharmaceutical companies need to develop new process to produce the drug in India. The innovator companies usually patent a large number of processes so as to prevent others from manufacturing the product. Eli Lilly protected its anti-infective drug Cefaclor through 32 processes and Ranbaxy managed to develop a new process which gained Ranbaxy international fame. MNC’s control over the Indian sector got a big set back by the policy. Indian pharmaceutical sector observed a vast expansion. Subsidies and infrastructural facilities given by the government enable the expansion and spread of the industry in various states. This was the glorious period for the sector in India. Number
of new products in cardiovascular, neuro, psycho-somatic, gastro renal, antifungal and anti-inflammatory segment were launched. The sector started more exports of the product. Many more organizations were able to get USFDA and WHO certification.

By the change of government policy not only the sector got huge boost but also there was a great control for monopoly of MNCs. Contribution of the MNC was dropped closer to 50 per cent by 1980s.

To increase private companies in the sector, government revised the policy in 1986 by relaxing lot of regulations with which number of private players increased in the sector with huge competition and hence due to lack of proper orientation the sector suffered industrial sickness.

However domestic drug prices in India were among the lowest in the world. The country also considered to be the low cost producer in the international market. Number of production units in the sector increased ten fold more within the 40 years. Growth of the sector continued till 1995 with continuous growth of more than 16 per cent. By 2010, 70 per cent of the country’s demand for bulk drug, chemicals, formulation etc was fulfilled by Indian pharmaceutical companies. Adoption of new technologies, scientific approach towards research and development led the Indian pharmaceutical sector at 3rd rank in the world in terms of volume and 14th in terms of value. The sector was immerging as global leader. A PriceWaterhouseCooper’s (PWC) report stated the value of the sector would reach US $ 74 billion by 2020. The achievement as the global leader could possible only by sharing hands of the Indian government, public sector and private interpreters.

The growth of Indian pharmaceutical sector is described as above. The glorious journey of pharmaceutical industry is also associated with few controversies. One of the WHO report stated that about 35 per cent of the fake drugs produced were from India. India’s global image got deemed by this report. Global also witnessed the Thalidomide episode in 1957.
Indian government became more cautious about the quality of medicine and implemented certain rules in its new drug policy to follow good manufacturing practices to produce good quality products as per the WHO standard.

The Indian sector along with global sector is changing rapidly with downward pricing pressure in the established market on one hand and increasing cost due to regulatory, competition and innovation on the other. The industry is being forced to look few methods to cope up the problems. To fulfill the society needs and sustain in the market the industry has to adopt new technologies, systematic way for the research and production. Pollution is also the major issue which needs to address. Indian government has taken sufficient steps to have a control over this and avoid future problems. Current industries not only from India but from the world are taking certain precautions for the synthesis of the chemicals and API’s.

To continue the growth and achieve the global requirements the sector has to come up with systematic approach in terms of research and process development. Substitute of hazardous chemicals, optimal use and recoveries of solvents, minimization in the wastes produced by the chemical operation, time cycle are some of the aspects to be looked in to. More and more institutes and industries are now focusing on the process development with technological skills. The thesis mainly deals with such developmental procedures.

Some of the examples prove that the world pharmaceutical sector is focused on process development. EPA Green Chemistry award was given to Lilly research lab in 1999. They produce Talampanol for treating epilepsy and neuro-degenerative diseases. Only three products isolation are associated for the seven step process. As much as 300Kg of chromium waste per 100 kg API is eliminated from the process. Chiral alcohol is obtained by bioreductive method with more than 99.9 per cent purity with more than 96 per cent yield. With this the process could minimize the waste, save energy, the overall yield increased from 16 per cent to 55 percent. And hence the process became cost effective.
In 2002 Pfizer Inc modified the process for Sertraline which could eliminate use of 140 metric tons of titanium tetrachloride per year which means the elimination of 440 metric tons of solid titanium dioxide waste.

One of the well-known and mostly accepted methods of resolution using some chiral auxiliary for the synthesis of chiral entities have always drawback of getting half of the material as a west. This is effecting on not only the overall yield but the generated west could be the major problem as a chemical west which need to be treated as it could be very harmful for environment. Use of ligands and organometals could have a very little chance to take up the synthesis on higher scale as the reactions and reagent itself are very sensitive and not user friendly.

These all promoted us to propose and develop a new method which could allow taking up the synthesis on multi kg scale considering the economy factor.

Second chapter of the thesis discusses about the synthesis of substituted α-methyl chiral benzyl amine derivative and extension of this approach for the total synthesis of Rivastigmine tartarate which is being used in the treatment of Alzeimer diseases.

The same approach is extended for total synthesis of calcimimetic NPS R-568: a type II calcimimetic compound that acts on parathyroid cell calcium receptor to reduce plasma levels of parathyroid hormone and calcium.

The molecules with cyclic sulfonamide moiety are gaining continuous attention because of their potent biological properties and their wide utility in drug designing for treating Alzheimer’s disease, Parkinsons disease and liver disease. Use of such structures found in designing of antiviral drugs also. Beside their clinical use they are also well utilized as chiral reagents and auxiliaries. These properties imparted high recognition for their efficient, scalable and economical synthetic routes.

In the third chapter process for the synthesis of few sultams is developed. The silent feature of the process includes use of commercially available starting materials and reagents, user friendly reactions with high yield. The process is not only environmental free but also economical on scale.
Organic carbamates are an important class of compounds having wide applications in pharmaceuticals and agrochemical industry. They are generally used for the protection of amino groups to form structurally diverse intermediates of biological importance. The recent past carbamates has seen keen interest from pharmaceutical industry for the development of drugs and prodrugs. The classical method for the preparation of carbamates includes the Hoffmann rearrangement, Curtius rearrangement and Lossen rearrangement reactions. There are several other methods to synthesize carbamates like with the help of phosgene, by reductive carbonylation of aromatic nitro compounds, by the oxidative carbonylation of amines, by using metal/non-metal carbonates/bicarbonates and by using carbondioxide . Although there are several reported methods for the synthesis of the carbamates, still there is scope to improve the existing procedures. The existing procedures are hindered with limitations like long duration of reaction, insignificant yield, and handling of toxic and hazardous chemicals, requirement of special type of reactors and skilled persons to handle these reactions.

Efficient, safe and economical method on commercial scale for the synthesis of carbamates of 2-amino pyridine and use of these for alkylaminopyridine on scale introduced in chapter three. The chapter also deals with synthesis of cyanohydrine derivatives and their reduction. Formation of cyanohydrine and substitute the hydroxyl with fluoro for acetophenone and benzaldehyde are well known in the literature. But the use of sodium cyanide on the scale prevents to take the process for the scale up. Use of TMS-cyanide with various Lewis acids to protect the hydroxyl as –OTMS and substitute it with fluoro using DAST in the same pot reported in the literature. The overall yield varies with the change in Lewis acid. Here we used indium(III)chloride which proved very advantageous in terms of reduction in reaction time with improvement in yield. More over handling of this Lewis acid is very easy compared to others.

Reduction of the nitrile to get amine with all the traditional methods like Raney nickel, Palladium, LAH could not yield the product. In all the cases the fluoro got replaced with hydrogen. Sodium borohydride alone or with calcium carbonate, cobalt chloride, AlCl₃ or Borane either not reduced the nitrile or yielded in multiple products.
The issue is successfully handled by reducing with sodium borohydride using cerium(III)chloride. Over all the process became feasible for scale up.