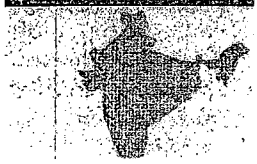


New Drug Development in India

By **K. Nagarajana** and **S. Rajappa**

Health care in the Indian subcontinent had been traditionally based on indigenous systems of medicine, especially Ayurveda, Siddha, and Unani, involves herbomineral remedies. The Western or allopathic system relying mainly on single chemical entities took roots in the country in the earlier part of the 20th century. Although an indigenous pharmaceutical company was started in 1901, the industry was dominated for quite some time by multinational companies (MNCs). These MNCs started slowly at first, but later the movement came close to an avalanche. This was largely due to the restrictive Indian Patent Act of 1970, which denied product protection to drugs and afforded only protection of processes and that too for a limited period of 7 years from the date of filing or 5 years from the date of sealing. This discouraged innovative MNCs from filing patents on original research products in India.

Simultaneously, the establishment of several universities, technological institutions, and national laboratories in India ushered in a formidable technological competence to re-engineer chemical products. This enabled enterprising Indian companies to synthesize contemporary drugs patented elsewhere by the innovators, formulate and market them within the country competitively and very often before the innovator MNC could introduce it. Quite often these Indian-designed processes featured novel chemistry and hence led to process patents. This factor — as well as the Indian Government's Drug Price Control regulations on selected essential medicines — resulted in the country enjoying one of the lowest prices for drugs in the world.

So from a small beginning, the Indian pharmaceutical industry's turnover in 1997-1998 was about Rs.120 billion or USD 3 billion. While the value works out to be about 1% of the world turnover, probably it may be as high as 9% in terms of volume, considering the low prices of drugs in India. The country is practically self-sufficient in respect of most synthetic drugs.

While the Indian pharmaceutical industry made tremendous strides, especially in the last two decades, with the required capital investments in plants to produce drugs and their formulations, significantly there has been no equivalent concern for new drug development in India. Historically the reasons have been the high costs involved, lack of interest among innovative MNCs to establish yet another research center in India, especially in a hostile patent climate after 1970, the relatively low turnover of national pharmaceutical companies and lack of a vibrant research culture in the industry.

However, after January 1995 — when India signed GATT and agreed to respect TRIPS and to amend its patent laws on drugs to align them with those of the West — the situation has changed dramatically. MNC discoveries will get full product protection for up to 20 years from January 1995. Assuming a 10-year development period from that day to time of registration — from 2005 onward — such new drugs will be out of bounds for others. This has prodded some of the bigger Indian companies to invest seriously in new drug development. The Indian government also has set aside a modest sum to be administered by the Department of Science and Technology to support the efforts of private industry in drug discovery in collaborative projects with public sector institutions. Previously it offered few marginal incentives to the industry for original R&D work.

Set up by Ciba Basel through Ciba India in 1963, Ciba Research Centre was the first full-fledged unit in the Indian private sector. This was practically self-sufficient with respect to various aspects of new drug development. It had a multidisciplinary team consisting of synthetic and natural product chemists, biologists, toxicologists, a metabolism group, a team of clinical investigators, and extensive animal house facilities. It had programs in the area of cardiovascular diseases, CNS disorders, diabetes, inflammation, fertility, hookworm, amoebiasis, bacterial infections including TB and viral diseases like small pox and influenza. Soon Ciba of India became Hindustan Ciba Ltd. and later Hindustan Ciba Geigy Ltd. After the last merger, the Research Centre narrowed down its priorities to parasitic infections including amoebiasis and filariasis, fertility control, and the discovery of new anti-tubercular agents. Sarabhai Research Centre, set up at Baroda a couple of years later, had a limited engagement in new drug development.

Launched in 1972, Hoechst Research Centre, Bombay, began modestly but soon grew into an equally strong institution with the requisite multidisciplinary team for new drug development. In the earlier years, its emphasis had been on

cardiovascular diseases, metabolic disorders, antiinfectives and rheumatism-related arthritis, and chronic inflammatory conditions. In recent times, it has laid emphasis on isolation of new molecules from natural sources such as plants and microorganisms. An advanced dereplication technology has been put in place in order to eliminate known compounds at an early stage and to facilitate the isolation of new active constituents. Currently, it has evolved into an *in vitro* target-oriented screening center for drug discovery while retaining its post-discovery developmental setup and expertise. Smith-Kline and French (SKF) had set up a research center in Bangalore exclusively for screening and culturing soils for discovery of new antibiotics, while Boots had established a moderate facility in Bombay to synthesize, screen, and develop drugs mainly for diabetes and amoebiasis. Of the four mentioned above, the research units of Ciba, SKF, and Boots have been closed in recent years for various reasons while that of Hoechst has been sold to an Indian group, the Piramals.

A singular exception to the rather dismal downturn in the MNC efforts in India for new drug development is Astra, which set up Astra Research Centre in 1986. Recently this has become a fully owned subsidiary of Astra Biochemicals Pvt. Ltd. This well-equipped center has a team of molecular biologists, molecular biophysicists, biochemists, and synthetic organic chemists and all requisite ancillary facilities including an animal house. The center has been focusing on antituberculosis, broad spectrum antibacterial, and antimalarial projects, identifying pathogen-specific macromolecular targets and developing robust assays for high throughput screening. The enzyme transglycosylase involved in the cell-wall biosynthesis of bacteria, two homologous sigma subunits of Mycobacterium tuberculosis and the enzyme Hypoxanthine-Guanine phosphoribosyl transferase in the malarial parasite are some of the targets that are being successfully used for discovering drugs at this center.

As noted earlier, a number of Indian companies have taken up the challenge of new drug development to face the post-GATT scenario. Dr. Reddy's Research Foundation set up by Dr. Reddy's Laboratories and Cheminor Drugs, for instance, was started in 1984 as Standard Research Centre. It acquired its present name in 1992 when it moved into an ultramodern complex near Hyderabad. Set up at a cost of USD 6 million, it has a multidisciplinary scientific team, fermentation facilities, and an adequate animal house. Its discovery research program focuses on cancer, diabetes, dyslipidemia, obesity, and bacterial infections. The center screens both synthetic compounds and those derived from natural sources and has facilities for combinatorial chemistry, molecular modeling, and drug design.

Ranbaxy Limited, Delhi has set up a similar large facility near Delhi with the emphasis on cardiovascular diseases, anticancer, and antiinfectives. Among other research centers set up by Indian companies to develop new drugs may be mentioned those of Cadilla Health Care, Ahmedabad (cardiovascular drugs), Dabur, Delhi (anticancers), and Wockhardt, Aurangabad, which have invested a few million dollars each. Lupin Laboratories, Bhopal and Torrent Pharmaceuticals, Ahmedabad are also reported to have high investments in research. A few companies have a more limited engagement, like Recon, Bangalore (anti-inflammatories) and SPIC Pharma R&D Centre, Maraimalai Nagar, Tamilnadu, (antituberculars). The numbers are likely to swell in the coming years. For example, U.S. Vitamins has announced the setting up of a biotechnology research center near Bombay.

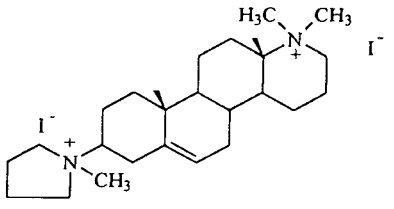
While many companies have registered their interest in new drug development, the expenditure as a percentage of turnover is still in the single digits, mostly less than 5% in contrast to the MNCs' average figure of 15%. The constraint has been mainly the comparatively lower profitability of the Indian companies engendered by stiff market competition, price controls in certain areas, and fragmentation. There is a move now in India as elsewhere in the world for consolidation by mergers and acquisitions. Coupled with the relatively low turnover of even the most successful companies (USD 250 million), individual investment in research for new drugs turns out to be a small figure in the international context. However, given the lower cost of trained manpower in India, this is adequate for discovery research for candidate drugs but insufficient for development to international standards. Licensing out the leads to MNCs and joint development are some of the approaches adopted by at least one Indian company to overcome this disadvantage. In this context, many companies like Dr. Reddy's Research Foundation, Ranbaxy, Recon, and SPIC have collaborative projects with national institutions for new drug discovery with somewhat modest funding for the latter by the Indian Government's Department of Science and Technology.

Among institutions engaged in drug development, pride of place should be given to Central Drug Research Institute belonging to the Council of Scientific and Industrial Research of the Indian Government. Inaugurated in 1951, the institute is equipped to discover new drugs and develop them to the marketing stage. Major areas of interest recently have been antifertility, cardiovascular, and CNS disorders (including memory loss due to aging), filariasis, malaria, leishmaniasis, and microbial infections. Expertise includes not only development of NCEs but also fermentation, vaccines, and diagnostics. The institute also has an extensive programme for screening natural products as sources for new therapeutic agents.

Many other institutions in India are engaged in various areas of biomedical research but without the total set up needed for new drug development. Some of these are:

- Indian Institute of Chemical Biology, Calcutta, which was established in 1935 as the first un-official biomedical research institute in India and taken over by CSIR in 1956 (bacterial and parasitic infections, genome mapping of *V. cholerae*, live oral vaccine for cholera, diagnostic for leishmaniasis, identification of markers for diagnosis and prognosis of malignant neuroectodermal tumours, chemistry of bioactive substances).
- Centre for Cellular and Molecular Biology, Hyderabad (basic research in cataract, DNA finger printing, development of a salt-inducible expression vector system for gene cloners wishing to express proteins in prokaryotic systems).
- Central Institute of Medicinal and Aromatic Plants, Lucknow (mainly devoted to genetic improvement, cultivation, production, and chemical processing of economically important medicinal and aromatic plants such as *Artemisia annua*) has considerable engagement in detection and characterization of new antimicrobial,

FIGURES 7, 8, 9, 10, 11, 12



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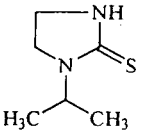

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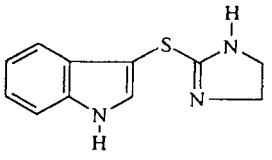

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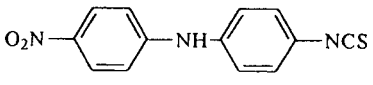

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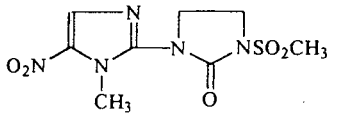

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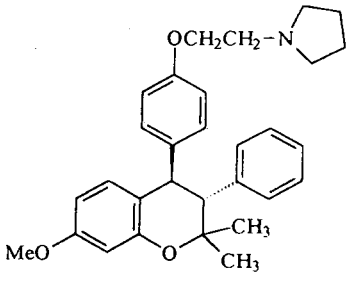

12

adenylate cyclase) although it could not be registered as a positive inotropic and antihypertensive drug. Recombinant erythroopoietin used especially in cancer treatment and renal failure therapies has been developed by an Indian company and is ready to be marketed.

Among new chemical entities that hold promise as drugs may be mentioned an insulin sensitizer structurally related to troglitazone, which has been licensed out, an amidine22 as an antidiabetic, a semi synthetic camptothecin derivative with anti-cancer activity, and an alpha1A uroselective adrenergic blocker derived from lactam chemistry for which an IND is to be filed for the treatment of benign prostate hyperplasia. Two quinolone anibacterials with promising activity are under development.

In terms of areas of engagement, the efforts of private industry will continue to be focused on indications like hypertension, diabetes, inflammation, anti-infectives, and cancer. For the moment at least, there is only one solitary private laboratory working on resistant malaria and tuberculosis. Visceral leishmaniasis (Kalazar) calls for urgent solution but there are no takers. Obviously, anxiety to earn profits takes precedence over attention to a compelling national health need. India has become a leading host for AIDS, but no concerted effort is still underway in the private or public domain to discover and develop affordable drugs that have to be necessarily priced considerably lower than the currently available reverse transcriptase or protease inhibitors.

What is the prognosis for Indian efforts in new drug development? Traditionally organic chemists in India have been strong both in synthesis and natural products. Additionally, they have to be trained in combinatorial chemistry and computer-based drug design. This has to be supported by high-throughput screening. Apart from a few contributions like a monkey model for petit mal epilepsy and adaptation of the human hook-worm to neonatal hamster, there have been few contributions from Indian research to new biological models for drug development. The future may see more of these. Work on recombinant DNA-engineered therapeutic peptides and oligo nucleotide-based drugs is yet to take roots, although there have been some recent claims of significant progress like the DNA vaccine for hepatitis-B being developed by Sanjay Gandhi Post Graduate Institute of Medical Sciences, Lucknow. Small molecules will continue to be important in new drug development in the foreseeable future.

Through the efforts of the Indian Government's Department of Biotechnology, a concerted attempt has been made to impart knowledge in molecular biology with gratifying results. Thus, scientists with experience in r-DNA technology and cloning are slowly becoming available. These are the kingpins in providing the receptors and enzymes that are needed for high-throughput screening.

What is perhaps the most important outcome of such efforts is the Good Laboratory Practice, which requires a determined and continuous effort to standardize and document chemical and biological experimentation and toxicological studies. Equally important is Good Clinical Practice. It is interesting to note in this context that Pfizer and Roche have started clinical research centers in India. Indian attempts to develop new drugs will be viable only if international markets can be accessed. GLP and GCP for the developmental activities and GMP for the production side are important issues to be tackled before the resultant products will gain international acceptance. Fortunately, the industry is getting ready to address these problem areas and to integrate itself successfully in the global search for new drugs.

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