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RECENT DEVELOPMENTS IN THE DRUGS AND PHARMACEUTICALS IN INDIA

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The pharmaceutical industry is an R & D intensive industry and the development of technology is crucial not only to its growth but also to the control of market which may also be influenced by other factors like brand names, patent protection and aggressive marketing etc. Adequate R & D is also necessary to provide the necessary backup for meeting the national health care objectives and targets. It may be important to note that production of more than 90 new bulk drugs has been initiated in the country post 1972 after the new Patent Act of 1970 came into force (Fig. 1). It is also pertinent to note that India stands amongst one of the technologically most advanced countries in the developing world for drug production capabilities according to a classification by UNIDO.

R & D in the Indian Pharmaceutical Industry and Technology Development

R & D in this sector is carried out with two distinct objectives :

(1) Development of new drugs, and

(2) Development of process technology for known drugs.

Because of the constraints of their operation, size and high cost of innovative drug research, most Indian companies cannot invest much in their R & D. Though there has been a constant increase in the R & D expenditure in the pharmaceutical sector (Fig. 2), the inputs available have restricted most of the R & D efforts in the Indian Drugs & Pharmaceutical Industry, largely to development of technology for known drugs. Break up of R & D expenditure is not available for the last few years to permit a detailed analysis. In 1982-83, there were only 9 pharmaceutical companies spending Rs. one crore or more on R & D. About 20 companies spent more than 2% of their sales turnover on R & D. In the Indian private sector, 34 companies spent about Rs. 20 crores. There were about 22 foreign sector companies in India spending about Rs. 14

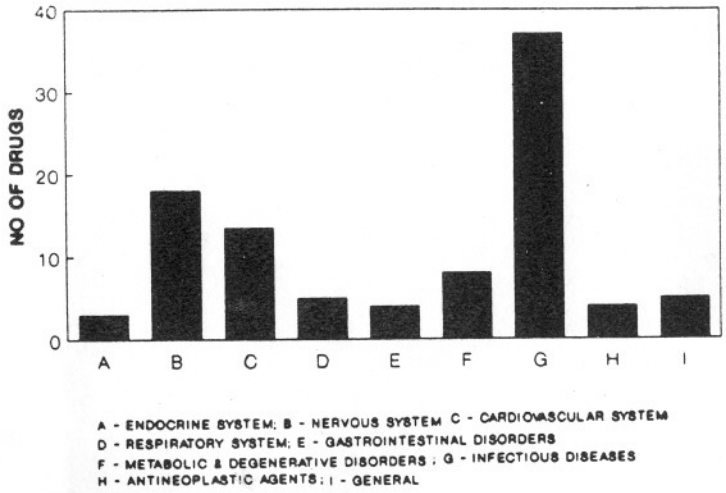

Fig. 1 : Indigenously developed drug technology in different therapeutic groups.

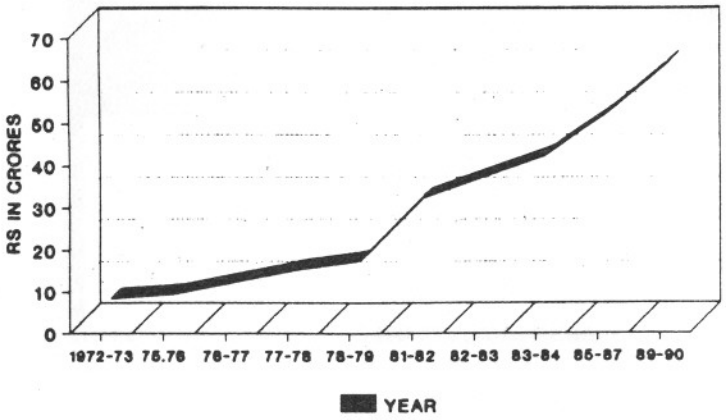

Fig. 2 : R & D expenditure in the pharmaceutical industry.

crores and the seven major public sector companies spent about Rs. 3.5 crores. Besides, there are several laboratories of the CSIR which spent more than Rs. 10 crores on R & D related to drug industry. The total expenses on R & D in 1982-83 amounted to 2.7% of the total formulations sale in that year. These inputs have resulted in indigenous development of technology for many drugs as well as development of some new drugs.

Impressive as these figures may seem, but when compared to R & D by the major Transnational Pharmaceutical Companies (TNC) in the world, the share of Indian companies is insignificant. Thus, the R & D expenditure by top 10 pharmaceutical companies of the world is more than total formulation production in this country (Table 1). Obviously, Indian companies have to focus their efforts into selected areas to make a significant impact.

Table 1 : Global R&D expenditure of major drug houses (1989)

Company	R&D ($ million)	R&D as % of sales
1. Hoechst	590.0	15
2. Glaxo	575.0	13
3. Sandoz	450.0	14
4. Bayer	450.0	12
5. Johnson & Johnson	390.0	17
6. Bristol-Myers	370.0	15
7. B-Ingelheim	376.0	19
8. Rhone-Poulenc	330.0	13
9. ICI	300.0	15
10. ER Squibb	270.0	12
11. Indian Drug Industry	035.0	2

New Drug Development

It should be noted that so far as new drug development is concerned, the Indian picture has not been particularly bright (Table 2). Most of the new drugs have been developed by CSIR and other public sector laboratories — a couple of R & D labs of foreign sector companies have also been active in this direction and have contributed two new drugs. One of these companies has since closed its R & D centre while yet another TNC subsidiary has started a new R & D centre largely devoted to Biotechnology (BT) research. There are 18 more new drugs likely to emerge as a result of indigenous R & D in the near future and several of these are at advanced stage of clinical trials or are awaiting registration. Most of these have been developed by CSIR laboratories, particularly the Central

Drug Research Institute, Lucknow. The results indicate that the Indian effort has been more cost-effective than even that of the developed countries. Though none of these drugs might have made any significant impact on the world pharmaceutical market, even this achievement cannot be rated as marginal, considering the meagre investments in R & D by Indian companies or even the public sector laboratories, as compared to those by TNCs, world-wide. Still the introduction of gugulipid, a lipid lowering agent obtained from *Commiphera mukul,* as a result of joint efforts by scientists of NCL, Pune and CDRI, Lucknow has been listed as one of the major new drug introductions in the concerned year on the global scale. It is to be hoped that this situation will change with increased turnover in the Indian Pharmaceutical Industry so that sufficient funds could be diverted towards basic R & D for development of new drugs.

Table 2 : New drugs developed in India

Drug	Year	Use	Institution
Urea stibamine	1921	Kala-azar	Trop.Med., Calcutta
Methaqualone	1956	Hypnotic	R.R.L., Hyderabad & K.G.M.C., Lucknow
Peruvoside	1958	Cardiotonic	C.D.R.I., Lucknow
Hamycin	1961	Antifungal	H.A.L., Pune
Centimizone	1972	Anti-thyroid	C.D.R.I., Lucknow
Sintamil	1976	Anti-depressant	Ciba-Geigy, Bombay
Tromaril	1980	Anti-inflammatory	R.R.L., Hyderabad
Isaptent	1985	Pregnancy termination	C.D.R.I., Lucknow
Nancy Kit	1985	Pregnancy detection	H.A.L., Pune
Cibemid	1986	Anti-protozoal	Ciba-Geigy, Bombay
Gugulipid	1986	Hypolipidemic	C.D.R.I., Lucknow
Filaria	1986	Diagnostic kit	C.D.R.I., Lucknow
Centbucridine	1987	Local anaesthetic	C.D.R.I., Lucknow
Centbutindole	1987	Neuroleptic	C.D.R.I., Lucknow
Centchroman	1989	Contraceptive	C.D.R.I., Lucknow

Indian Patent Law and Development of Pharmaceutical Technology by the Indian Industry

While patenting in a given field does give some indication of the level of technological innovation in the field, patents are more often used as means of

A change in the Indian Patent Act 1970 restricted the patenting only of process in the field of Drugs and Pharmaceuticals and that too for a short period of 5 to 7 years. This encouraged many Indian companies to develop alternative process technologies for production of a large number of drugs (Fig. 1). As a result several drugs could be produced in India even before their international patents expired (Table 3). This allowed early entry of new drugs in the Indian market and since the alternative processes broke the monopoly of the international patentee, these were also available in Indian market at comparatively much lower prices. In atleast one case, it helped to bring down the price of the newly introduced drug very significantly even in the international market. In many cases, this has been possible due to development of more efficient process technologies as well as due to increased competition resulting from horizontal transfer of technology which was encouraged by this change in the Indian Patent Act.

Table 3 : Drugs in two therapeutic groups for which alternative process technology was developed indigenously despite patents in USA

	Therapeutic groups/drugs	US patents expiry in	No. of companies
A.	Cardiovascular		
	Atenolol	1994	5
	Diltiazem	1991	2
	Metoprolol	1995	2
	Minoxidil	1992	2
	Nadolol	1996	1
	Nifedipine	1989	4
	Propranolol	1990	1
B.	Antihelmintics		
	Albendazole	1995	1
	Fenbendazole	1993	6
	Mebendazole	1992	6
	Pyrantel	1990	2
	Tinidazole	1988	5

Contribution of the Public Sector

The introduction of public sector in the country was the consequence of a conscious philosophy which wanted to achieve the following three objectives:

(3) not only to achieve self-sufficiency in drug production but also to achieve an exportable surplus and earn foreign exchange.

An additional objective of these units, implied in the attainment of 'Self-sufficiency, was to undertake production of bulk drugs from a more basic stage thus evolving a backwards linkage in technology generation. While the first and this additional objectives have been met to a significant extent, others have only been marginally met. Detailed recommendations were made by the Hathi committee to achieve these targets but effective steps remain to be taken.

The Public Sector Companies set up in-house R & D centres not only to ensure efficient absorption of the imported technology but also to ensure improvements in these technologies and generate new technologies. In so far as technology adaptation and generation has been concerned, the performance of this sector has been largely satisfactory. Of course, this could always be improved if suitable steps were taken consistently *viz.*, the action proposed in the new drug policy of 1978 could have been implemented more vigorously ensuring avoidable duplication of R & D efforts on one hand and ensuring better coordination with the national laboratories on the other.

Hindustan Antibiotics Limited (HAL) was the first Public Sector unit to be set up. It not only developed a new anti-fungal antibiotic Hamycin but improved upon the existing technologies. The largest public sector unit is, however, the Indian Drugs and Pharmaceuticals Ltd (IDPL). According to available reports, IDPL has improved upon the imported technology in 14 cases and has developed better processes in 10 cases, leaving only 7 cases where the imported technology could not be improved (mostly antibiotics). Moreover, it is producing 25 new bulk drugs, and 15 intermediates based on the indigenously developed technologies. It has also perfected pilot scale technologies for another 15 drugs. It is important to note that both these units as well as the Bengal Immunity are also involved in basic research to develop new drugs. A new non-steroidal anti-inflammatory drug being developed by IDPL is at advanced stages of clinical trials. The most important gain is the production by public sector companies of many drugs from a basic stage. There is, however, little collaboration between these units and their linkages with the national laboratories and academic institutions are far from satisfactory.

CSIR Laboratories and Drug Development

The CSIR has been playing an important role in technology development in many sectors and the Drugs and Pharmaceutical (D & P) is certainly one of the more successful areas of effort. There are several laboratories of the CSIR which are actively engaged in drug research. While this is the major area

production. The National Chemical Laboratory (NCL) has developed technology for production of at least 25 drugs and intermediates.

The major objectives of CSIR in this area have been :

(a) discovery fo new drugs and prophylactic agents for diseases of special relevance to the country,

(b) systematic scientific investigation of plants and traditional remedies for their use as drugs, and

(c) development of technology for indigenous production of drugs and pharmaceutical products.

Recently, CSIR laboratories have also been involved in developing drugs from marine fauna and flora. The thrust areas of CSIR in new drug development include:

—drugs for population control;

— drugs and prophylactic agents for parasitic and microbial infections including immuno-diagnostics;

— drugs for cardiovascular and central nervous system disorders;

— drugs for metabolic disorders;

— immunomodulators; and

— making better use of known drugs such as throguh drug targeting and new dosage forms or delivery systems.

For achieving these objectives, CSIR has undertaken R & D programmes in its various constituent laboratories and it also provides financial support to research in academic institutions.

CDRI has already released for marketing seven new drugs and an immunodiagnostic (Table 2) besides developing production technology for a number of known drugs. A brief list of important drugs whose technology was developed by CDRI and the company which adopted the technology is given in Table 4. Thus, these laboratories have contributed significantly into developing technology for known drugs as well as developing new drugs. Several of these laboratories have won national awards for the innovators as well as for the industry utilising it. In some cases like L-ephedine and dextropropoxyphene, the total requirements of the country are being met and surplus is being exported.

The CSIR efforts are being increasingly directed to novel synthetic systems like

Table 4 : Drug technologies developed at CDRI

Sl. No.	Name of drug	Company
1.	Clofazimine	Astra-IDL, Bangalore
2.	D-2 Amino butanol	Themis Chemicals, Bombay
3.	Dextropropoxyphene HCl	Wockhardt Pvt. Ltd., Bombay
4.	5-6 Dimethyl benzinidazole	K. Methaqualone & Chemicals, Lucknow
5.	L-Epherdine-HCl	Malladi Drugs & Pharmaceuticals Ltd., Madras Altus Pharmaceuticals, Bombay
6.	N-Methyl, Piperazine	Chemopharma Pvt. Ltd., Bombay
7.	Paracetamol	Duphar Interfran, Bombay
8.	Pyrithoxin	Themis Chemicals, Bombay

Other important drugs for which processes have been developed/released include : Indomethacin, Amitriptyline, Ampicillin, Clonidine, Bacampicillin, Cyclophosphamide, Sulphamethoxazole, Ibuprofen, Trimethoprim, Primaquine, Pseudoephedrine

*Others also

laboratories are also involved in developing new drug delivery systems and dosage forms. With the setting up of Institute of Microbial Technology, the focus on biotechnological products is also becoming more evident. Several laboratories have concerted programmes of developing new immunodiagnostics and they have already achieved limited success. The diagnostic kit for filaria developed by CDRI has already been commercialised. CDRI developed conjugates of steroidal sex hormones have been utilised to produce enough antibodies for meeting the total national requirements of RIA kits for the next decade.

Challenges and Opportunities in the Pharmaceutical Sector

Though Indian pharmaceutical industry has made big strides in the last two decades, it faces still bigger challenges as also opportunities. While the industry has established a self-reliant base for synthetic drug technology, several large tonnage drugs continue to be imported. If necessary technology is developed, the country can also have large exports of many of these drugs (Table 5).

Fermentation Technology

A large number of antibiotics are being produced in the country with imported or indigenous technology. The first penicillin was produced in India by Alembic Chemicals using indigenously developed technology. Several β-lactam antibiotics and other semi-synthetic penicillins as well as other drugs like L-ephedrine are today produced partly by fermentation and partly by chemical synthesis. The country is still totally dependent on imports for most of the newer antibiotics and a number of other fermentation products. There is ample scope

for improving upon existing fermentation technology in the country. The developed countries have almost totally switched over to continuous fermenters with automated computerised controls whereas most of Indian producers still use batch fermenters. The use of immobilised enzymes or microorganisms to increase the efficiency of biological conversions can offer competitive technology in many cases.

Table 5 : Some large tonnage and newly emerging generic drugs

Large tonnage	Newly emerging
Chloramphenicol	Albendazole
Doxycycline	Amoxycillin
Emetine	Atenolol
Ephedrine	Cephalexin
Ethambutol	Colxacillin
Frusemide	Ciprofloxacin
Ibuprofen	Danazol
Mebendazole	Enalpril
Metronidazole	Famotidine
Methyl Dopa	Metoprolol
Nalidixic acid	Norfloxacin
Paracetamol	Ofloxacin
Propranolol	Piracetam
Sulphamethoxazole	
Tetracyline	
Trimethoprim	
Tinidazole	

Biotechnology

Recent developments in Biotechnology have offered many new drugs. Some of these *viz.* Interferrons, Tissue Plasminogen Activator (TPA) or Erythropoietin are now manufactured through Recombinant DNA (R-DNA) technology. In addition, some of the conventional drugs like Insulin and Growth Hormone are also manufactured by R-DNA technology. Thus many substances which were hitherto manufactured chemically can now be biologically produced in a more efficient manner by genetically engineered microorganisms. The world is fast moving towards 'Tailored Vaccines' or protein engineering for developing new enzymes and antigenic proteins. The Indian industry is far behind. There has been a significant change with the creation of a full-fledged Department of Biotechnology by the country which is launching several coordinated

Table 6 :Therapeutic group-wise worldwide introduction of new chemical entities during 1983-1988

	Therapeutic groups/drugs	No. of introductions
1.	Endocrine system	13
2.	Nervous system	56
3.	Cardiovascular system	42
4.	Respiratory system	15
5.	Gastrointestinal disorders	18
6.	Metabolic & Degenerative disorders	68
7.	Infectious diseases	56
8.	Anti-neoplastic agents	9
9.	General	5
	Total	**282**

Even the approach to research for development of standardised ethical products from these systems has to change from isolation and development of single constituents as drugs. The current strategy being followed at CDRI and other institutions for ICMR and CCRAS research projects of standardizing semi-purified preparations of the traditional formulary are likely to be more rewarding. Our approach of broad-based biological screening has also given good results. Mention has already been made of the development of Gugulipid through such approach while several others like Curcumin and Picroliv are under clinical trial. We are following a similar approach for screening marine fauna and flora to identify medicinally active products. In view of the vast area and different agroclimatic zones being available, India is in an advantageous position to exploit these resources.

Conclusions / Perspective

The discussion in the preceding paragraphs has illustrated how the Indian Drugs and Pharmaceutical industry is at the threshold of a technological take off. Our self-reliance in Bulk-Drug Technology for a large number of synthetic drugs has not only increased our export to both the developed as well as developing countries, but several companies have established joint ventures in various developing countries like Nigeria, Thailand, Sri Lanka, Malaysia, Singapore and Indonesia, etc. (Fig. 5).

There is an increasing awareness to our weaknesses in the sectors like fermentation based drugs, biologicals and vaccines etc. Recent spurt of interest in the area of Biotechnology by both public funded research institutions as well as by industry is a definite indicator. Similarly, the efforts to get the necessary

expertise in developing new drugs through Computer Aided Designs and developing new drug delivery systems is promising. Our approach to develop ethical pharmaceuticals based on rich repertoire of traditional knowledge has started paying dividends. There are indications that new drugs from our marine fauna and flora may become available in the near future.

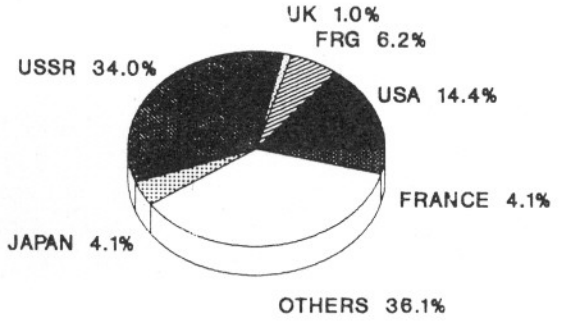

Fig. 5 : Patterns of Major Indian Exports

While Indian technologists and indigenous industry have the advantage of its balanced Patents Act of 1970, our constraints are also several. First of all the total size of Indian industry ($ 1700 million) itself cannot generate adequate funds required to develop new drugs and the research in public funded R & D institutions with limited resources cannot compete either with the international industry. They must, therefore, increase their turnover with exports to both the developing as well as developed countries in selected areas (*viz.* synthetic drugs, biologicals and drugs based on traditional medicine). Moreover, our drug industry cannot be internationally competitive in the absence of an adequate support from basic chemical and petrochemical industry for its raw material needs. It is creditable that drug industry in India could develop to its present level even before adequate development of the chemical and petrochemical industry. With the available expertise in the industry and with other advantages like those of low cost of labour, willingness of national R & D Institutions to work closely with the industry, vast natural resources etc, it is necessary for the industry to carefully select its product mix, put in venture capital and resort to aggressive marketing to place India on the global map in this area.

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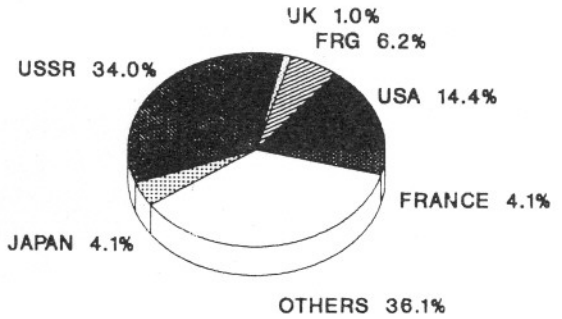

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