Past, Present & Future :

INDIAN PHARMACEUTICAL INDUSTRY

K. Nagarajan,
R & D Centre, Searle (India) Limited, Thane-400 601.

Introduction :

"Medicines for the Masses" and "Health for all by 2000 AD" have become familiar slogans in the Indian subcontinent. The pharmaceutical industry constitutes only a small part of healthcare, nevertheless it enjoys high visibility and attracts widespread attention, since in the public perception, swallowing a pill is one important, probably the most important part in the treatment of an ailment. This has been evidenced by the national reactions to the deliberations of the Hathi Committee on drugs, the Patent Act 1970 on Health Products reverberations of which are even now felt, the Drug Price Control Order 1987 and its aftermath. Being primarily concerned with the health of the populace, official policies and pronouncements on drugs have tended to be populistic, bordering occasionally on the irrational. Since the end of this century is but a little over a decade away and we have set ourselves ambitious goals, it is time to ponder over the past, present and future of this scenario.

Growth of Pharmaceutical Industry in India :

The dimensions of the Chemical Industry in India prior to independence were very modest; since then it has taken giant strides, having currently an annual turnover of well above Rs. 25,000 Crores. Of this, the pharmaceutical industry which can be considered to be concerned with speciality chemicals contributed Rs. 2690 crores in 1988-1989 by sale of formulations from a bulk drug production worth Rs. 530 crores. This was achieved with an investment of Rs. 750 crores through well over 9000 units – small scale, large scale, national, multinational, private and public, employing about 2,00,000 persons directly and 10,00,000 indirectly in related or ancillary industries. In 1952-1953, this industry had a capital investment of only 24 crores through 1750 units producing bulk drugs worth about Rs. 10 crores and formulations of about Rs. 40 crores. Comparison of these figures helps us realize that the growth indeed has been phenomenal.

Projected Estimates of Future Requirements :

The "Health for all by 2000 AD" slogan of the Indian Government had envisaged production of formulations to the tune of Rs. 16,000 crores from drugs valued at around Rs. 4,000 crores calling for an investment of perhaps Rs. 6,000 crores at the dawn of the 21st Century. The NCAER projections also gave a figure of Rs. 8300 crores formulations to be manufactured in 1995 at the end of the 8th plan. A joint working group of OPPI and IDMA has made an indepth study of the demand forecast for 1995 and arrived at a figure of Rs. 6,610 crores of formulations (at 1989 prices) from bulk drugs worth Rs. 1,350 crores, calling for an investment of between Rs. 1950 – Rs. 2200 crores. The additional requirement could thus be between Rs. 1200 – Rs. 1450 crores, representing double the present investment.

Government Policies on the Pharmaceutical Industry :

The policies embodied in various licensing policies and drug price controls, laudable as the objectives may have been, have resulted in a virtual choking of the pharmaceutical industry. DPCO 1987 promised much relief but this has been slow in forthcoming. With prices of drugs firmly pegged and costs of inputs rising continuously, margins have dwindled as evidenced by the profit before taxes of the industry falling from 15.47% in 1969-1970 to 3.4% in 1986-87. Drug prices in India as of today are one of the lowest in the world – for example the Indian price of a strip of 10 tablets of metronidazole, a popular antiamoebic drug, is Rs. 2.76 against Rs. 5.74 (Pakistan), Rs. 6.74 (Srilanka), Rs. 25.54 (UK) and Rs. 43.52 (Indonesia). It may be also noted that price increases on Indian drugs have not kept pace with increase in prices of commodities – the index is 222.4 for drugs in 1987-1988 as against 418.4 for all commodities in relation to base 100 in 1970-1971.

The result has been many units becoming sick while a number of others have managed to keep their heads above water by diversifying into allied fields like pesticides. It must be also said to their credit that some units have fluorished

even in the midst of these adverse circumstances.

However, there is some evidence that the DPCO 1987 which has a somewhat more rational categorisation of drugs and pricing formula will slowly improve the situation, as it is administered progressively more equitably and judiciously. Nevertheless, the problem requires more sustained and urgent attention if the pharmaceutical industry which has several creditable achievements to its credit has to deliver the goods expected of it. In fact, the government may be well advised to abandon all controls and let market forces play, reserving for itself the right to intervene stringently if things go out of hand. We are even hearing nowadays statements about privatisation of the public sector which would have been looked upon as blasphemy earlier!

Strengths and Weaknesses of the Indian Pharmaceutical Industry :

The technological strength of the industry and its R & D base are fairly sophisticated, thanks to high availability of trained personnel. More than 225 bulk drugs are produced indigenously, many of them with locally developed knowhow. This has been largely due to the Indian government's policy of promoting indigenisation and import substitution, although multinational units have also contributed significantly by bringing in their knowhow and expertise. The industry has also received some aid from the national laboratories in process development. As remarkable achievements of the industry can be mentioned the fact that they have developed locally process knowhow for top-selling world class drugs like cimetidine (anti-ulcer), nifedipine (cardiovascular), piroxicam (anti-inflammatory), diclofenac (anti-inflammatory), diazepam (anxiolytic), amoxicillin (antibacterial), α-methyl dopa (anti-hypertensive) and co-trimoxazole (antibacterial). The industry has been able to manufacture indigenously, drugs with complicated structures requiring multistep synthesis like diphenoxylate (antidiarrheal), steroidal derivatives including microbiological transformation products, chiral molecules like d-naproxen (anti-inflammatory) and semi-synthetic β-lactam antibiotics like cephalexin using immobilized enzymes. They have been also successful in manufacturing and introducing state-of-the-art drugs like norfloxacin (antibacterial), taking advantage of the patent policy of the Indian Government.

In the international arena, Indian industry has been able to manufacture and export competitively some generic drugs like ibuprofen, metronidazole, trimethoprim, sulphamethoxazole and ethambutol, observing good manufacturing practice. The exports recorded for 1988-1989 were Rs. 400 crores, consisting of Rs. 243 crores of bulk drugs including quinine salts and Rs. 157 crores of formulations, medicinal castor oil being excluded from the figure. And the prospects of increasing the exports are brighter. In fact India is the largest producer of some of the bulk drugs in the world.

On the debit side may be mentioned a few weaknesses. While there is no doubt that Indian R & D has been able to develop processes for known drugs, this has been largely by following or adapting published literature. The innovative component that would fetch internationally sustainable and exploitable patents has not been in much evidence; nor has it produced any significant new drug. This theme will be expanded in the article later. Secondly, the country has made very insufficient progress in fermentation technology required for life saving antibiotics. While a few like penicillin are manufactured locally, the strains do not have international yields; and Indian production is way below its needs. In a few cases, like rifamycin SV, we have no indigenous production at all. Recently granted licences may hopefully redress the situation.

Largely due to these and other factors, our import bill in 1987-1988 has been Rs. 350 crores, bulk drugs amounting to Rs. 234 crores and the rest, formulations. For the period cited, our import of bulk drugs would thus amount to nearly 50% of our own production!

The sectoral reservations of drug manufacture propagated by the government have not been helpful. Small scale production units are often not cost effective. Antibiotics were reserved for public sector, but finally the government has relented in the face of reality and allowed it to be diluted to joint sector. The role of the public sector in bulk drug production and formulation, originally intended to give it a commanding position, so far has been useful only in a limited, social sense and has not been exactly a roaring success in terms of the real market.

Finally the higher costs of inputs compared to the international situation and lower productivity of labour also constitute hurdles for the industry in giving a better performance. This in fact would partially explain the fact that our exports cater barely to 0.1.% of the world pharmaceutical market of about Rs. 170,000 crores.

Status of R & D in the Indian Pharmaceutical Industry :
Process Development for Known Drugs :

The successful performance of the Indian R & D effort highlighted earlier acquires greater significance when the meager investments are considered. The figure for R & D expenditure in the Indian Pharmaceutical Industry in 1986-1987 was Rs. 50 crores, representing 2.3% of the turnover in that year (Rs. 2140 crores), which was higher than the 0.7 % for the chemical industry as a whole. Nevertheless this is way below international figures which range between 7-23% (e.g. Glaxo 11.2%, Bayer 22.5%). It may be argued that the latter represents the cost of innovative research (R) while ours is only development (D). However, rapid obsolescence of drugs elsewhere would require our industry to develop processes for newer drugs,. study their formulations, carry out some clinical studies and incur marketing expenses for successful introduction. Even this would call for a higher order of investment in R and D than the one currently obtaining. However, the present level of profitability (3-5%) would be a deterrent, as would be obvious if we compare it with international data (Glaxo 28%; Merck 28.4%; Abott 30%).

Apart from the relaxation in price controls promised by the DPCO 1987, the Indian Government has incentives like IT

exemption of 100% revenue and capital expenditure incurred by R & D, import under OGL of capital equipment and research chemicals and more recenty exemption from price control for 7 years of drugs produced by indigenous R & D using innovative technology resulting in cost-effectiveness. These are palliative at best. There are other irritants like high duties on imported equipment and chemicals. It is imperative that the government should remove these hurdles and also offer further relaxations in price controls if the industry has to acquire a high enough profit margin to invest in R & D adequately.

Given adequate monetary inputs, the Industry's R & D should be able to augment their performance and contribute to increased production. It may be noted especially in this context that international patents on a large number of drugs (14 of the top 15) will be expiring in the next few years (1995) presenting an opportunity for increasing our exports.

In their endeavours, scientists should take judicious advantage of recent developments like high pressure reactions leading to products of different regio and stereochemistry compared to atmospheric pressure reactions. Sono chemistry seems to be worthy of attention in heterogenous reactions, especially those involving free metals. Induction of optical activity using homogenous chiral catalysts or chiral auxiliaries is in commercial usage abroad already. Natural and 'artificial' enzymes for induction of chirality on an industrial scale seems to be a possibility very soon in the developed countries. These can be incorporated into our production processes advantageously wherever applicable.

Apart from process development, formulation of bulk drugs is an important aspect of manufacture. Our R & D adequate expertise for classical formulations. Breathtaking advances are taking place abroad in this field such as transdermal preparations, zero order delivery systems, liposome and antibody tagged preparations for targeted delivery. A recent announcement claims an orally active preparation of insulin. Those advances which are cost effective need to be studied for introduction in the country.

Similar efforts are needed in the area of packaging also.

Basic Research for Development of New Drugs :

While the scenario for process development of known drugs is thus rosy in India, the story is altogether different in the area of new drug discovery. It is now well known that the latter requires a multidisciplinary effort deployed over a long period and is bedevilled both with uncertainties of reaching the market stage as well as with rapid obsolescence once a new chemical entity has been introduced as a drug. Estimates of the cost of developing a new drug vary from time to time and country to country but seem to run into Rs. 100 crores currently. Investment in drug discovery research both in the private and public sector in India has been perfunctory and marginal, forming a smaller part of the 2.3% of turnover mentioned earlier. Central Drug Research Institute, Lucknow and Indian Drugs and Pharmaceuticals Limited, Hyderabad are public sector institutions involved in this exercise, while there are only two now in the Private Sector.

The enormous monetary requirement for drug discovery, the long gestation period and the relatively meager resources of units of Indian industry are continuously cited as causes for reluctance in investment. In fact one of the foremost and earliest research centres of Indian private industry was closed recently with the management citing as causes inordinately large expenditure and insufficient returns at present and in the foreseable future. An additional important reason given was the changing character of the drug discovery process and their inability to attract relevantly qualified scientists. Inadequate patent production for new discoveries was also implicated.

Nevertheless, it is the author's contention and plea that we should pursue new drug discovery more purposefully and under certain conditions it will be possible as well as profitable.

It was mentioned earlier that the global drug production in 1987 was Rs. 170,000 crores, to which we contributed a sorry 1.6%. A more optimistic or perhaps realistic way of looking at it would be to correct our figure for lower drug prices obtaining in India. If we do this against the average UK price of 8 drugs as a standard, we get a higher factor of 2.5 bolster our turnover. Even by the normal reckoning, as recently as in 1985 we had the eighth largest pharmaceutical market in the world. Argued in this fashion, new drug development may become more affordable. An alternative way of looking at it would be to appreciate that the cost of new drug discovery and development in India could be less, although one must concede that costs will be the same for registration and introduction abroad for drugs of any nationality.

We do have a large number of trained chemists who can pick up the expertise needed for the art and science of drug development. On the other hand we have a shortage of biologists and biochemists with the right training. Facilities for breeding animals under standard conditions for testing for activity and particularly toxicity would call for sizeable investments, the requirements being mainly for international registration. Conditions are somewhat less stringent for Indian registration. Part of this problem will be alleviated if our biologists take advantage of innumerable in vitro assays which are being developed abroad to reduce if not eliminate use of animals for test purposes in the face of mounting antipathy of an activistic section of the public.

In the choice of areas or indications for drug development, it must be our aim to select those that have not only relevance to our needs but also have an international prevalence. A simple calculation of costs and market size will make it immediately obvious that for such an activity to be viable research must be directed to capture a share of the world market.

Antibacterials or anti-infectives will be the first choice, since they are in considerable demand all the world over including India. The worldwide revenues of this category in 1987 amounted to about Rs. 20,000 crores ($ 13. 6 billion or 12% of the total market) with a significant growth potential. The Indian sales in 1988 were more than Rs. 400 crores,

amounting to about 20% of the toal turnover of the industry and had a growth rate of 17.4%. A drug discovered and developed in India would be a gold mine even if it succeeded in securing but 1% of the global catch. Antibiotics obtained by fermentation and manipulated to produce semisynthetic derivatives dominate the antibacterial group. While our weakness in fermentation will be a handicap, our expertise in process development of the semisynthetics like cephalexin can be easily exploited to construct newer molecules. Of course, when we deal with purely synthetic drugs like the quinolones, norfloxacin, we should be entirely at home. Following the initial discovery of antibacterial activity of nalidixic acid, molecular manipulation led to oxolonic acid and so on, until a really hot lead was obtained in the form of the first fluroquinolone. Since then in the short span of a few years, essentially analogue chemistry has provided a bunch like norfloxacin, pefloxacin, lomefloxacin, ofloxacin, tosufloxacin and tomufloxacin and will continue to do so for some years. The financial rewards have been a billion dollar in sales in 1988. It should be very well within the capacity of our scientists to develop comparable molecules, if necessary, using computer assisted QSAR or molecular modelling. While the assay of *in vitro* and *in vivo* activities against a spectrum of bacteria again falls within the area of our expertise, we would need more training and orientation to perform sophisticated analysis of mechanisms of action such as DNA gyrase inhibition by quinolones.

A few other areas of national and international relevance in regard to medical needs and market potential (along with their global sales in 1987) are : Cardiovascular agents ($ 16 billion), nonsteroidal anti-inflammatory agents ($ 5.3 billion); antiulcers ($4.6 billion); Zantac, the leading brand of ranitidine, alone brought $ 1.48 billion in 1987; sales have since then exceeded ($ 2 billion) and anticancer compounds ($ 3. 9 billion). In many of these areas, we may not be able to produce the first path breaking drug like the first beta-blocker or first antiulcer agent. However, given the leads like nifedipine, captopril, ibuprofen, naproxen and cimetidine, it should be possible for us to design newer patentable analogues with marketable activity. But speed is essential; slow and steady will not win this race.

It is pertinent to point out in this context that Japan, a small albeit industrially advanced country, has been a late comer in the field of new drugs, but has already established a leadership position. For the past seven years, Japan was the country where the greatest number of New Chemical Entities (NCE) were introduced for the first time in the world as drugs, the figure for 1988 being 14 out of a global total of 52. Only a few of the research-based Japanese companies are of world-class size, most of them being small to medium. Nevertheless they have made their mark internationally by licensing their discoveries to or codeveloping them with the mightier multinationals. Some recent successful illustrations are famotidine, diltiazem, norfloxacin, lomefloxacin and several semi-synthetic cephalosporin antibiotics.

For the Indian situation it is suggested that private industrial units who can afford investments of Rs. 4-10 crores, alone or preferably in association with institutions like Central Drug Research Institute (in fact there may be a need at least initially to have a few more of the latter but with better market appreciated and business orientation) should develop drugs in these areas for Indian registration; they should also collaborate with willing multinationals for worldwide development and registration, with the bigger partner shouldering the larger burden for this work. For successful ventures of this kind, we may have not only to shed our phoebia of multinationals, but also make necessary changes in our Patent Laws for the sake of reciprocity. A beginning must be made at some point in time to test viability of this proposal.

Drug development research in India should also pay attention to filariasis and resistant malaria. Apart from chemotherapy, vaccines may also be attempted. In fact, this should be an important goal of biotechnology in this country, while academic research can explore the isolation of therapeutically active peptides like TPA, Interleukin and Insulin by rDNA technology. Lastly research should also be targeted towards discovering safe and easy to use antifertility agents. In this area the mifepristone lead could serve as a potential lead.

The possibility of using our abundant plant sources to derive Ayurvedic drugs is receiving increasing attention in the country. A potentially successful approach would be to get a well characterized extract from a single plant (rather than multiple ones) and to establish its activity by bioassays and modern clinical investigations and to present it in a dosage form with adequate quality assurance backup. The country will watch the Guglip (active extract of gum guggul having the guggulsterones with anti-hyperlipidemic activity) experiment with interest. However, it is unlikely that such an approach will have international acceptance at the moment. The more successful classical concept which still prevails is the isolation of a single active ingredient, its manufacture by large scale extraction or synthesis and presentation in standardised dosage forms. Some of the popular examples are quinine from the cinchona bark, reserpine from Rawoulfia serpentina and more recently, vinblastine from the periwinkle.

Conclusion :

Indian Pharmaceutical Industry has successfully catered to the drug requirements of the country at reasonable costs and can live up to the future demands provided certain beneficial measures are taken. An important contributory factor to the performance of the industry has been the strength of its R & D which has been particularly successful in elaborating indigenous processes for a large number of drugs. New drug discovery has not so far received adequate attention, but it is possible and necessary to nurture it. A useful approach would be to concentrate on a few areas of national and international relevance and opt for collaborative arrangements to target the global market. Success in this venture will not only contribute to human welfare but also enrich the coffers of the nation and fetch it a measure of respepctability commensurate with its size and stature.