BULK DRUG SCENARIO IN INDIA

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The dimensions of the Chemical Industry in India prior to independence were very modest; since then it has taken giant strides, posting a current annual turn over in excess of Rs. 25,000 crores. Of this, the pharmaceutical industry which can be considered to be concerned with speciality chemicals contributed an estimated Rs. 2690 crores in 1988-89 or about 30,000 formulations by 14,000 formulators. In 1987-88 for which figures are available, the industry employed a capital of Rs. 650 crores and about 2,00,000 persons directly and 10,00,000 indirectly in related or ancillary industries. Bulk drug production is expected to rise to Rs. 607 crores in 1989-90 and formulations correspondingly to Rs. 2800 crores.

The technological strength of the industry and its R & D base is considerable. Of the 350 bulk drugs produced indigenously, locally developed know how accounts for a significant slice. In fact it is gratifying to note that the country has the largest production in the world of a few drugs like ethambutol, sulphamethoxazole, trimethoprim and α–methyl DOPA. This has been due as much to the Indian Government's policies as to the enterprising spirit of the pharmaceutical industry and the increasing sophistication of its technical manpower has been developed indigenously for all drugs with sales in excess of $ 300 million worldwide in 1985, such as cimetidine, ranitidine, piroxicam, diclofenac, naproxen, diazepam, amoxicillin, α-methyl DOPA, cotrimoxazole and cephalexin. Recent additions to this list are the quinolone antibacterials such as norfloxacin and ciprofloxacin. Even after discounting for some exaggeration, the residual achievements are very creditable indeed! Among the nonantibiotic drugs, d-naproxen and α-methyl DOPA are chiral and the present synthesis involves conventional resolving agents. Cleavage of penicillin G by immobilised enzymes leads to 6-APA which is utilized directly for amoxicillin and via ring expansion to 7-ADCA for cephalexin. Sophisticated molecules like diphenoxylate (antidiarrhoeal) are

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produced involving multistep operations, as also steroidal derivatives including microbial transformation products. In fact UNIDO experts have categorised the Indian Pharmaceutical Industry as being at the top of group 5 whose characteristics include near self sufficiency in raw materials, capability to produce from basic stage, bulk drugs belonging to a wide range of therapeutic groups, competence in R & D and presence of an effective distribution system.

Impressive as all these achievements may appear to be, it is to be noted that the industry is still far from fulfilling the 7th plan target of production of bulk drugs and formulations of the value of Rs. 1,330 and 3,775 crores respectively. The causes are many, the major one being the government's restrictive pricing policies and these have been discussed in various articles and forums. The revised DPCO 1987 having fewer drugs under price control and offering larger MAPE for categories 1 and 2 has afforded the industry considerable relief from the chocking grip of the earlier price controls which had pushed several units into the sick list. Even now considerable delays aggravated by inconsistencies and vacillations are experienced in the revision of prices. However, it can be expected optimistically that the process may pick up speed once proper ground rules are laid in detail and accepted.

A new measure of encouragement has been announced by the government offering exemption for 7 years to bulk drug manufacturing units from the DPCO, 1987. These pertain to drugs produced from the basic stage by a process developed through own R & D. The exemption covers processes which are significantly different from the know-how or technology available in the country leading to import substitution or cost reduction. It remains to be seen how far this will be successful since two factors have to be borne in mind: 1) there has been hardly any innovative process discovered in the country and 2) for some bulk drugs. the competition is so fierce that market forces will keep the prices down even if the government would allow a higher price for the inventor. It is a pity that the BICP has turned down the drug industry's plea for more financial incentives for larger investments in R & D.

Much has been written about the performance of the industry in the export of bulk drugs and rightly so. This has risen from Rs. 33.4 crores in 1985-86 to Rs. 240 crores in 1988-89 which is expected to go up further to Rs. 280 crores in 1989-90. The list of exports includes sulphamethoxazole, trimethoprim, ampicillin, doxycycline, erythomycin, nalidixic acid, metronidazole, mebendazole, α -methyl DOPA, ibuprofen, danazol, chlorpheniramine and tolbutamide, some of them to the tune of several tons. In fact we saw earlier that the country is the largest producer of some of these drugs in the world. Publicity has been also given widely and justly to a few manufacturing units having been approved by FDA, USA from the point of view of GMP.

This success has been undoubtedly largely due to the entreprenurship of the producers and they do deserve the country's accolade. But we need to bear in mind that this has been possible also because of the sizeable export incentives offered by the Indian Government but for which these products would not be competitive in the international market. Secondly, many of the export incentives offered by the Indian Government but for which these products would not be competitive in the international market. Secondly, many of the exported drugs have become generic and industry in the developed countries tends to move away from producing low value, high volume generics to high value innovative drugs. Thirdly apart from the low wages of the country, it is quite likely that our investment is much less than that of the West in effluent treatment and pollution control and that the West would welcome developing countries like India taking up 'dirty' drug chemistry as in the case of dyestuffs. It may be also mentioned that despite the dramatic increase in export of bulk drugs, the country has not achieved the plan targets.

It is often proclaimed that the country's Patent Act 1970, restricting protection of drugs to unitary processes and that too for a period of 5 years from the date of sealing of the patent (or 7 years from the date of filing whichever is earlier) has been largely responsible for the dramatic growth of the Indian Drug Industry and for its export performance. A close examination of the issue will show that this is of limited validity. A substantial part of the production of bulk drugs for local consumption as well as for export pertains to generic drugs for which no patent protection exists and hence no infringement is involved. A few 'patent-alive' drugs have been introduced in the country taking advantage of the fact that either the investor did not file a patent application in India or the patent term has expired. In the case of most such introductions, the bulk drug is being imported by formulators, the country incurring significant outgo of foreign exchange. Of course there is a miniscule number of honourable exceptions who have developed indigenous but not necessarily innovative knowhow. Export of such drugs to the West and Japan would not be possible because of valid patent protection in those countries; but this is possible and happens to a limited extent to a few third world countries.

There is no gainsaying the fact that the Patent Act 1970 has been largely useful to us to the extent of making available some very recent drugs, eg. ranitidine and norfloxacin. Prices would be naturally lower than elsewhere since neither the foreign supplier nor the local producer who developed own process knowhow incurred even a fraction of the 100 million dollar bill for the discovery of a new drug. It is but natural that the research-based inventing companies, some of which spend on their R&D efforts nearly half the amount or more of our pharmaceutical industries' turnover, should bring pressure on us through their governments to change the situation using various forums like GATT and instruments like the Omnibus Trade and Competitiveness Act. The natural instincts of our scientists, as of those elsewhere, will also tend towards respecting intellectual property, unlike those of the entrepreneurs. It has become mandatory and it should be possible to find a compromise solution that would be fair to all concerned. As the fortunes of our industry grow and multiply to the point of being able to afford more innovative research for developing new drugs, we shall ourselves recognise the need for such protection. At any rate, our patent laws urgently need tightening to prevent the horizontal transfer of indigenously developed technology which is happening on a large scale in India today and has led to the mushrooming of bulk drug production as a cottage industry, notably in Andhra Pradesh.

While the success of the export story is well known, our ever increasing import of bulk drugs is not so well recognized. the bill was high as Rs. 285 crores in 1986-87 and is estimated to be Rs. 345 crores in 1987-88. Penicillin G, penicillin V and formyl refampicin are some of the important imports, pointing to a serious weakness in the country's bulk drug scenario (see later). Others are drugs like sulphadiazine and mefenamic acid. A few items like metronidazole, mebendazole, paracetamol and trimethoprim are also imported to supplement local production. It is not clear whether the import bill includes drug intermediates like isobutylbenzene (ibuprofen), 6-APA, 7-ADCA and D- phenylglycine (all for semisynthetic penicillins and cephalosporins) whose cost is substantial.

The record of the country in the discovery and development of new drugs has been lacklustre and has been discussed by several authors including the present one. Among the drugs of indigenous, origin enfenamic acid, a NSAID, has been withdrawn for lack of efficacy. Sintamil, an antidepressant, continues to perform modestly; centbucridine, a local anaesthetic, centbutindole, an antipsychotic and guggulipid, and antihyperlipidemic are recent introductions whose performance is to be watched. Except for Sintamil, the other drugs have been discovered and developed in CSIR laboratories. The involvement of the Indian private in-

dustry in new drug development is meagre and has been confined to multinationals. Hoechst, CIBA-GEIGY and SKF had sizeable commitments, the last one limiting itself to antibiotics. Of these, the CIBA-GEIGY and SKF research centres have been closed, leaving the first as the sole survivor. But given the country's scientific talent and prospering pharmaceutical industry, especially members of the so called 'national organised sector', a fresh look at the issue is warranted. A large number of opinion makers however believe that at the present stage, the Drug industry can afford and needs to concentrate on only process development. But even for this limited goal, increased investment in R&D will be useful. The drug industry's figure of 2% of the turnover is larger than the average for Indian Chemical Industry but is much less than that of the international input.

Given proper monetary inputs, some of the more important aspects of development of bulk drugs would be : 1) the choice of the drug to be produced - there should be an identified need for the drug in the country and/or there should be good export potential 2) In either case, the market should be attractive, ensuring reasonable returns on investment 3) Production technology should be available or enough R & D expertise should exist for development of a process and 4) Suitable equipment for production in the required scale should be available. Except for glass-lined kettles for which there is a waiting period, the country is fairly self-sufficient in this respect, although we still depend largely on imports for sophisticated electronic analytical equipment. The availability of organic chemical starting materials is limited and these are expensive. Most of them are imported. However, the situation is slowly improving even as our petrochemical industry grows.

Process development by R & D should be initiated after a thorough literature survey of various available approaches. the right choice should be arrived at after trial experiments on the better ones and should be dictated by various considerations such as indigenous availability of raw materials, ease of operations, minimal polluting effluents, yields, costs, etc. In scale up operations it is advantageous to associate at an early stage, production chemists and plant chemists and plant chemical engineers so that proper viable technology can be developed and transferred suitably. Effluent treatment and elaboration of analytical controls for intermediates and final products are also in the domain of R & D scientists at this stage. computer simulation of reactions and optimisation of parameters and automated feed back control devices for production are areas which need appreciation and adoption by the bulk drug manufacturers in India.

R & D Chemists in charge of development of bulk drugs in the country have been using fairly modern reagents and processes. thus they have replaced successfully in some cases, the older condition for alkylations such as aprotic solvents and hazardous sodium hydride or sodamide with biphasic aqueous, non aqueous systems, alkali and phase transfer catalysts. they could use judiciously with advantage, where appropriate, modern developments like high pressure reactions leading to different regio and stereochemistry compared to atmospheric pressure reactions. Sonochemistry seems to be gaining importance 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. The harnessing of 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 wherever applicable.

The field of biotechnology which covers the above area and also encompasses fermentation has developed dramatically all over the world. We do have some cases of microbiological transformations in bulk drug synthesis. We also have indigenous production of antibiotics like penicillin, tetracyclin, erythromycin and neomycin. Much of this is very unsatisfactory since our strains

yield considerably less than elsewhere. Consequently our antibiotics cost more and are in perpetual short supply. thus our production of penicillin G was 305 MMU in 1987-88 and is expected to be 500 MMU in 1988-89 against a demand of 1800 MMU now, 3500 MMU in 1995 and 5900 MMU in 2000. the present gap is met by imports of penicillin G and penicillin V which again has caused considerable confusion and furore. In its anxiety to rectify the situation, the government is planning to licence a few manufacturers, each for producing a minimum of 1000 MMU. This could create a surplus capacity and attendant problems.

Rifampicin is a similar story. We are the world's largest consumers (for TB and Leprosy) with an expected demand of 189 tons in 1990 going upto 700 tons in 2000. We have no basic fermentation but we import formyl-rifamycin which is coupled with imported 1-methyl-4-aminopiperazine to afford rifampicin. Thus we need to strengthen our fermentation capabilities on an urgent basis, fostering appropriate expertise and pumping in adequate resources. In this field as in every other area of bulk drug production, the government would do well to re-examine its policy of sectoral reservations.

It is interesting to note that cleavage of penicillin G to 6-APA using the immobilised form of the enzyme, penicillin G acylase is already being carried out in the country. Much of this is imported, although local knowhow has been developed. It is now reported that an Indian bulk drug manufacturer is going to put up a big plant for production of this enzyme for local use and export.

It would thus appear that Indian scientists and entrepreneurs are slowly but surely progressing in employing modern technology for bulk drug production. With increased relaxations and fewer controls from the government side and greater attention being paid to removal of some shortcomings and reinforcing certain areas by the industry there is ample reason to believe that the country would be able to satisfy all its bulk drug requirements and also be an important supplier to the world at large.