International Conference on Cinical Pharmacology & Therapeutics
Bombay, November 20-22, 1987

NEW DRUG DEVELOPMENT IN INDIA - SOME REFLECTIONS

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INTRODUCTION :

Man's incessant quest for knowledge has led to a stupendously large number of discoveries and inventions over the centuries. One of his most fascinating and challenging but historically more recent endeavours has been towards the development of new chemical entities as drugs, which has had a tremendous impact on society. The availability of drugs has resulted in a drastic reduction of morbidity and mortality and to an abundant improvement in the quality of human life. These exercises have led to a profound increase to our basic knowledge of living systems and augmented our awareness of the likely causes of their distortions and disruptions, at an increasingly more fundamental level. Further, a vigorous and ever-expanding drug industry is contributing to the coffers of various nations both directly by productive employment and indirectly by improving the health of the populations.

In an industry where products face a forbidding rate of obsolescence, basic research becomes essential for survival. Credited as we are with having one i.e. the largest technically trained man-power in the world on the one hand and on the other hand, having the second largest population with widespread incidence of tropical and other diseases, it becomes an interesting as well as important exercise to assesss what our contributions have been towards the development of new drugs. A primary requisite for such an appraisal is an understanding of the process for drug development.

PROCESS FOR NEW DRUG DEVELOPMENT :

The design and development of new drugs call for an array of costly and sophisticated inputs. It is complex and long-drawn out and requires a multi-

disciplinary team of chemists, biologists, toxicologists, biochemists and cians. The process begins with the identification of research progra and projects by drug development groups - industrial units, national la tories, medical centres, etc. taking into account the medical needs of environment, marketing opportunities and inputs, financial considerat national and company policies and contemporary insights into disease proce Action is then initiated in the chemical laboratory, where, after interac of chemists with biologists and based upon folk-lore medicines, biochem concepts or novel chemical ideas or insights, a new synthetic compounc a plant extract or a pure plant product is preapred.

These substances are then screened by a team of biologists in a variety animal models or other test systems for diverse indications. The discov of a lead which occurs once in a while, despite its rarity, serves as an impe to intensifying all round efforts. This lead is then optimised by molecu modifications based upon intuition, semiempirical or quantitative structu activity relationships and computer-assisted molecular modelling of speculati drug-receptor interactions. A candidate drug thus identified may be no one for a disease indication for which prior therapy did not exist; or f an indication for which treatment exists, it may promise an alternative appr ach with a different mode of action; or at the least, if it is an analog of an existing drug, it should show some quantitative and/or qualitative adva tages.

From this point onwards, drug development follows a well-recognized course Detailed biological and sub-acute toxicity data as well as some informatio on the biotransformations of the candidate drug in animals are submitte to the Drug Controller or equivalent regulatory authority for permission t carry out Phase I or human tolerability studies, using a suitable formulation Abroad, the studies are frequently carried out in-house, while in India the

must be undertaken in public medical institutions through approved doctors. Acceptable tolerability allows the transtition to Phase II trials involving dose searching for efficacy. These two studies are usually restricted to a small number of centres. Along with tolerability and efficacy data, bioavailability and human biotransformation information is also obtained in these studies. The clinical pharmacologists who are involved with these phases of drug development play a pivotal role, since their experience serves to give important feedback to the laboratory scientists concerning the suitability of the formulation and efficacy in relation to dose and blood levels. Many a candidate drug becomes a casuality at this stage, ostensibly because animal data often cannot be extrapolated to humans. Neverthless, the observant and perceptive clinical pharmacologist is in a position to suggest potentially useful modifications to the formulation of the trial drug or to its structure. It is quite possible and it has happened often that a drug would have failed in a given indication but clinical astuteness would have discovered a different therapeutic application.

Success in the dose-searching efficacy studies would lead the candidate drug being subjected to double blind trials at a few centres against an existing standard drug.

The candidate drug poised to enter Phase III multicentric trials then undergoes chronic toxicity studies. Its effects on reproduction would also be investigated. Ideally details of human absorption, excretion, distribution and metabolism would have been also obtained by now. Very frequently - more so nowadays than earlier - mutagenicity and carcinogenicity studies would be initiated, this being mandatory for certain classes of drugs. In parenthesis, it may be noted that in most parts of the West, strict adherence to Good Laboratory Practice conditions for all such studies is a must. Based upon the above information, permission to carry out the multicentric trials in a large number

of patients is obtained. Registration or marketing approval of the candidate drug is granted upon successful completion of these trials and acceptance of the total data by Drug Regulatory authorities.

With increasingly stringent regulations, the task of developing new drugs has become Herculean. Contemporary reports indicate that the introduction of a new chemical entity as a drug takes 10-12 years and costs about Rs.650 million ($ 50 million). The odds are in the neighbourhood of 1 to 15000 for a substance to become a useful drug, although Janssen pharmaceutica has been more successful (1/1000). The situation is further aggravated by the faster obsolescence of drugs as compared to other products of daily use.

DRUG DEVELOPMENT : THE WORLD SCENARIO:

Notwithstanding the forbiding dimensions of the problem unfolded above, interest and investment continue unabated, especially in the developed countries, in discovering newer drugs offering improvements over existing ones and conquering diseases which have survived such onslaughts so far. The efforts have been rewarded with rich dividends primarily in the form of useful additions to our therapeutic armamentarium. Equally importantly, the pharmaceutical industry with an estimated annual turnover of $ 150 billion is contributing substantially to material prosperity. Finally and most importantly, these endeavours have very significantly resulted in an increase of several orders of magnitude of our basic knowledge, pushing its frontiers to daring distances.

NEW DRUG DEVELOPMENT - THE INDIAN SCENE RESEARCH CENTRES AND AREAS OF INTEREST

Although there had been sporadic efforts earlier, the establishment of the Central Drug Research Institute in Lucknow, after the country attained Independence in 1947, may be considered to be the first serious attempt to create the multidisciplinary milielu with reasonable infrastructure needed for new drug development. The Indian Drugs and Pharmaceuticals Reserach Centre, a similar venture, appeared on the scene much later.

Regional Research Laboratories in Hyderabad and Jammu have also deployed some efforts in this area. In the Private sector, CIBA-GEIGY Research Centre founded in 1963, may be considered to be private industry's first serious and fully integrated venture. Sarabhai Research Centre in Baroda started somewhat earlier on a smaller scale is reported to have now abandoned its new drug development programme. Research centres of Hoechst and Boots in Bombay were started on a mere modest scale than CIBA-GEIGY, but are expanding slowly and steadily. Of the three, Hoechst has a programme on antibiotic research as one of its activities, while SKF Research Centre at Bangalore has it as its exclusive concern. In addition to these, there are various institutions in the country which are specialising in certain areas, with new drug development as a small component of their activities, eg. Foundation for Medical Research (leprosy), Indian Cancer Research Institute (Cancer) and Institute for Research in Reproduction (fertility) all in Bombay and Vallabhai Patel Chest Institute (Respiratory disorders) and National Institute for Communicable Diseases (malaria, filaria, etc.) in Delhi. Finally it may be mentioned that institutions like The All India Institute of Medical Sciences, New Delhi, KEM and JJ Hospitals, Bombay and King George Medical Hospital in Lucknow participate in new drug development processes with inputs during clinical trials as well as occasionally in earlier phases.

Among these, the Central Drug Research Institute has been working in several areas ranging from cardio-vascular diseases to bacterial and parasitic infections, handling both synthetic compounds and natural products while other Research Centres have been confining themselves to fewer indication, each one of them having some engagement in atleast one or two 'tropical' diseases - parasitic and bacterial infections. CIBA-GEIGY have disengaged themselves from involvement with plants while Hoechst has increased its emphasis in this area. The latter centre and SKF have commitments in antibiotic research, an area with which the R & D divisions of Hindustan antibiotics at Pimpri and Indian Drugs and Pharmaceuticals at Rishikesh are also involved.

RESULTS OF INDIAN EFFORTS :

We are now poised to look at the fruits of the endeavours of these institutions

over mainly the last 25 years.

Drugs that have been approved by the Drug Controller of India are listed below along with their indications:

Tromaril (Enfenamic acid)	Antiinflammatory
Sintamil (Nitroxazepine)	Antidepressant
Centbutindole	Antipsychotic
Centbucridine	Local anaesthetic
Guggu lipid	Antihyperlipidemic
Centimizone	Antithyroid
Methaqualone	Hypnotic
Taomex (Nonaperone)	Antipsychotic
Ancletol (amoscanate)	Anthelmintic
Varsyl (tinazoline)	Nasal decongestant
Cibemid (satranidazole)	Antiprotozoal
Hamycin	Antifungal

Among the above, Tromaril, Sintamil and Hamycin have been marketed for some years, with the first two selling for about Rs. 10 million each. Centimizone is available to the public, while centbutindole, centbucridine and guggu lipid have been just released to potential manufacturers. Methaqualone was synthesised in India, but the discovery of its therapeutic potential and further development took place abroad. The remaining four are unlikely to be marketed for reasons embracing marketing or medical aspects.

As the second level should be noted the following preparations which are in early or advanced clinical trials.

Centchroman	antifertility, antitumor (likely to be approved soon)
Centpropazine	antidepressant
Centperazine	antifilarial
Centazolone	tranquilizer

Centhaquin	*antihypertensive*
Curcumin	*antiinflammatory*
Forskolin	*antiglaucoma, positive inotrope*
Rhodorubicin	*antitumour*
Chandonium	*neuromuscular blocker*
A benzimidazole carbamate	*anthelmintic*
benzothiozole isothiocyanate	*antifilarial*

To this list may be added two vaccines, one for leprosy and another for fertility control. Although not new chemical entities, these vaccines are mentioned since they are products of biomedical research.

A few compounds with significant and interesting biological properties, which have advanced to preclinical toxicology may also be noted.

HL 707	*antiamoebic*
L 84 7667	*antimalarial*
Buquiterine	*antiallergic, bronchospasmolytic*
Ammonicins	*antibiotic*

Mention of course must be made that atleast 12 other preparations were taken to the clinic, but these failed to develop into useful drugs. The list includes 5 antihypertensives, an antidepressant, a hypnotic, two hypoglycemics, an antitussive - analgesic, an anxiolytic and an anti-small pox agent.

While numerically, the picture painted as above looks rosy, there is no room for complacency. It must be conceded that none of the approved drugs represents a major break-through. They are not world-class blockbusters such as Tagamet (cimetidine, antiulcer), Zantac (ranitidine, antiulcer), Naprosyn (naproxen, antiinflammatory) and Procardia (nifedipine, antihypertensive - antianginal) with 1986 sales in U.S. alone of $ 546, 480, 285 and 215 million respectively.

SOME RELECTIONS ON THE STATUS OF NEW DRUG DEVELOPMENT IN INDIA:

It is obvious from these figures that the achievements of the country are not commensurate with its size or requirements. An attempt is now made to analyze the reasons and offer remedial suggestions.

a. *Investment in new drug development :*

Available figures indicate that the Indian investment in R & D in Pharmaceuticals is around Rs. 400 million, out of which probably Rs. 150 million goes into basic research. This is in stark contrast to what a much smaller country like Japan spends on Pharmaceutical R & D. Thus in 1985, the figure for Japan was Rs. 30,000 million, out of which 17% or roughly Rs. 5100 million was allocated for basic research. Giant corporations like CIBA-GEIGY and SKF alone invest sums of the order of Rs. 4100 million in this field. The norms for investment in R & D in the developed countries is about 7-16% of their turnover (eg. Wellcome 13%, Warner-Lambert 16%, Japan 7%) while ours is at a piddling 2% - and this is already twice the average of the Indian Chemical Industries' investment in R & D ! Considering that new drug development is cost intensive, our lackluster performance is understanbly inevitable.

On the other hand, it must be borne in mind that our Pharma turnover in 1986-87 placed at Rs. 21,000 million (bulk drugs Rs. 4,600 million) is just about 1% of the world sales. The pharmaceutical divisions of several multinationals like CIBA-GEIGY have a turnover of around Rs. 50,000 million. Our figure does not even measure upto tiny U.K.'s performance at the same level in 1985.

The situation is aggravated further by the fact that due to various factors, including restrictive price control policies of our government, the profitability of our drug industry is very low with many firms slowly sliding into sickness. The balance sheets of two leading pharmaceutical concerns exemplify the malady - post tax profit of Rs. 50-60 million, at about 3-4% of their turnover. The gravity of the problem becomes immediately apparent if we consider the cost of developing a new drug as Rs. 600 million ! Astra Director, Peter Sjostrand's statement is particularly relevant to our situation - 'Minimum

level of profit at which a company can be competitive in our opinion is 20% of total working capital - 20-25% is a desirable profit level!'

It remains to be seen whether the newly announced modified Drug Pricing Policy of the Indian Government would remedy the situation. The first impression is not very optimistic.

The patent situation is also detrimental to significant investment in research since only processes and not products derive protection - and that too for a pitifully small period.

b. Manpower, scientific milieu :

Although India does have a vast pool of scientific/technical manpower, there is a dearth of people with the right kind of background in drug development, especially in biomedical sciences - biologists of various hues, biochemists, clinical pharmacologists, etc. the situation in Chemistry being slightly better. Even there, talent in synthetic chemistry abounds but weaknesses are apparent in expertise in applications of quantitative structure - activity relationships and computer-assisted molecular modelling both of which are integral to modern rational drug design. A considerable number of such people with the requisite training prefer to stay aborad.

There are very few institutions in the country which offer formal training for this vocation; it is mostly an inhouse exercise within drug development groups, although it must be mentioned that GS Medical College in Bombay uniquely offers a programme in clinical pharmacology for new drug development.

In contrast to the developed countries, the climate of vigorous, academic basic research in biomedical sciences that is a prelude to drug discoveries is lacking in India; nor is the country located conveniently in the international circuit of seminars and symposia which offer vicarious awareness of the latest trends and avenues for cross fertilisation of ideas. The country has barely woken up to the potentials of the explosive growth of genetic engineering and bio-technology.

Finally the cost of sophisticated tools indispensable to new drug development has become too prohibitive for the Indian Drug Industry, insult being added to injury by the Government in the form of import duty extending upto 140%. The Universities and National Laboratories are fortunately not crippled by this duty.

c. *Areas of Research:*

The need for drug development efforts in India to concentrate on 'tropical diseases' is a familiar and understandable issue. However, one tends to easily forget or overlook the fact that cost-effective drugs are already available to combat and control many parasitic and bacterial infections - helminthiasis, amoebiasis, malaria, tuberculosis and leprosy. Considering that our drug prices are some of the lowest in the world, if they are still beyond the reach of the poorest segment of the population, a certain measure of government subsidy becomes inevitable to reach these drugs to the masses. Resistant malaria and filaria still need adequate solutions - perhaps the vaccines in the horizon may be the answer to these challenges. Obviously, a more realistic solution to the problem lies in increased personal and community hygienic measures. Drugs to control fertility however do represent a crying need.

On the other hand, there is no doubt that increasing sections of the Indian population are afflicted with the diseases of the 'affluent'. Efforts in these areas are certainly not to be ignored or scoffed at. In fact they become necessary and justifiable if we consider the obvious fact that our drug development efforts will be profitable only if they are aimed at and succeed in capturing a share of the world market. The reality of a much smaller sales potential for tropical diseases cannot be wished away and, in fact, the only solution for the dilemma can be a heavy subsidy from the Government for research in these areas directly or indirectly through relaxation of pricing curbs.

Finally in this section should be noted that new drug development in India should not only stick to new chemical entities by conventional synthesis, but also try to exploit our plant resources, validating by modern techniques, some of the claims of Ayurveda, and other traditional systems of medicine. The emerging science of genetic engineering needs also to be harnessed for

the production of both vaccines as well as for the therapeutically active peptides and smaller molecules.

Conclusion:

The challenges of new drug development have assumed such formidable proportions that we cannot hope to grapple with them with our insignificant resources. That these processes have become internationalised are as much due to economic compulsions as to locational, logistic, tactical and strategic reasons. Our national interests and goals in the area of drug development would be best served by adherence to a global approach. Fears of multinationals using cheap labour in India or using Indians as guinea pigs have been frequently expressed. viz. the fulminations of Nature Correspondent against the Astra Foundation in Bangalore or the news reports on the Indo- US joint Vaccine Action Programme. Considering that multinational ventures such as these serve both our short and long term interests and that adequate safe guards against exploitation can be and are built into them at the governmental level, diatribes appear to be political phoebias, or unjustified over-reactions, if we give the critics benefit of doubt. On the other hand, multinationals investing in basic drug research in India have to ensure that they do not treat their Indian Centres as poor relations with a symbolic status, that they are treated as equal partners in a joint and noble venture, that they are also involved in profitable projects of international dimensions and that their research products reach a fruitful international status.

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Scientific research is not itself a science, it is still an art or craft.

WILLIAM H. GEORGE

Investigators seem to have settled for what is measurable instead of measuring what they would really like to know.

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